Review

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Review

The Interplay Between Mitochondria and Drugs: Molecular Mechanisms, Pharmacotoxicology, and Clinical Implications

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Abstract

Mitochondria, essential organelles involved in cellular energy production and various metabolic processes, are increasingly recognized as innocent bystander targets for many pharmaceutical agents. This review aims to highlight the complex interaction between mitochondria and drugs, covering the molecular mechanisms by which drugs affect mitochondrial function, their pharmacotoxicological effects, and clinical outcomes. We investigate how drugs can impact mitochondrial dynamics, oxidative phosphorylation, reactive oxygen species production, and apoptosis, resulting in either therapeutic benefits or adverse effects. Understanding these interactions is crucial for enhancing drug efficacy, minimizing toxicity, and developing novel therapies that target mitochondrial pathways in various contexts.

Keywords: therapeutic drug monitoring; mitochondria; clinical toxicology; drug safety; oxidative stress; ROS; mitochondrial disease; oxidative phosphorylation; Mitochondrial bioenergetics

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1. Introduction

Mitochondria are well-known organelles often called the "powerhouses of the cell" because they generate most of the cell's energy as adenosine triphosphate (ATP). However, beyond producing energy, mitochondria perform various interconnected cellular functions that are often overlooked in their molecular and clinical significance. Therefore, mitochondria are more than just "powerhouses"; they are dynamic, multifunctional organelles vital for maintaining human health and coordinating many physiological processes [1–3].

To clarify, besides producing ATP through cellular respiration, which powers nearly all cellular functions—from muscle contraction to protein synthesis and nerve signaling—mitochondria act as the metabolic hub for intermediary metabolism, including the citric acid cycle, fatty acid oxidation, amino acid metabolism, urea cycle, and heme synthesis. They also manage calcium balance and signaling, regulate apoptosis, generate and detoxify reactive oxygen species (ROS), support antioxidant defenses, produce heat through thermogenesis, alter mitochondrial structure through fusion and fission, and maintain overall mitochondrial quality via mitophagy. Additionally, mitochondria play a crucial role in innate immunity and inflammation by releasing danger signals (DAMPs) and aiding antiviral responses (MAVS) [4].

These various activities highlight the essential and complex functions of mitochondria in nearly every aspect of human physiology.

Notably, this diverse role in human physiology mirrors its function in disease. In fact, mitochondria are crucial in the development of many human illnesses, going well beyond traditional mitochondrial disorders.

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In fact, when these cellular powerhouses fail, the effects can spread throughout the entire body, leading to the development and progression of many chronic and degenerative conditions, including:

1.1. Neurodegenerative Diseases

Mitochondria are especially vital for neuronal health due to the brain's high energy demands .

- Alzheimer's disease: Mitochondrial dysfunction is an early and vital feature. It causes decreased energy production, increased oxidative stress, changes in mitochondrial shape and movement, and buildup of amyloid-beta within mitochondria, all of which lead to synaptic failure and neuron death [5,6].
- Parkinson's Disease typically involves issues with mitochondrial complex I, increased oxidative stress, and impaired mitophagy. Mutations in genes linked to familial Parkinson's, such as PINK1 and PRKN (also known as Parkin), directly affect mitochondrial quality control [5,6].
- Huntington's Disease involves mitochondrial abnormalities, including decreased ATP production, increased reactive oxygen species (ROS), and disrupted calcium balance, which contribute to excitotoxicity and neurodegeneration in the striatum [7].

1.2. Cardiovascular Diseases

Mitochondrial health is crucial for the high-energy cardiomyocytes (heart muscle cells).

- Heart Failure: Impaired mitochondrial bioenergetics, increased oxidative stress, and altered mitochondrial dynamics result in decreased contractility and ultimately lead to heart failure. Changes in fatty acid oxidation, the heart's primary fuel source, are also observed [8].
- Ischemia-Reperfusion Injury: During a heart attack (ischemia), lack of oxygen damages mitochondria. When blood flow is restored (reperfusion), a surge in ROS production and the opening of the mitochondrial permeability transition pore cause additional damage and cell death, which significantly affects recovery [9,10].

1.3. Metabolic Diseases

Mitochondria play a central role in cellular metabolism.

- Type 2 Diabetes: Mitochondrial dysfunction in insulin-sensitive tissues like muscle, liver, and fat contributes to impaired glucose and lipid metabolism, leading to insulin resistance and pancreatic beta-cell dysfunction. This involves decreased mitochondrial content, altered morphology, and reduced capacity for oxidative phosphorylation [11]
- Non-Alcoholic Fatty Liver Disease (NAFLD): Hepatic mitochondrial dysfunction, characterized by impaired fatty acid oxidation, increased ROS production, and altered mitochondrial dynamics, plays a key role in fat buildup in the liver and the development of inflammation (NASH) [12].

1.4. Cancer

The role of mitochondria in cancer is intricate and cannot be fully explained by the "Warburg effect," where cancer cells predominantly depend on glycolysis even when oxygen is present. In fact, mitochondrial function remains crucial for:

- Metabolic Reprogramming: Although cancer cells often exhibit altered mitochondrial respiration, this seems to be a reuse of mitochondrial metabolism to support rapid growth, including utilizing mitochondrial anaplerosis (replenishing TCA cycle intermediates) for biosynthesis [13,14].
- Apoptosis Resistance: Mitochondria are vital for programmed cell death. Dysregulation of mitochondrial apoptotic pathways can allow cancer cells to avoid death, which is a key factor in cancer progression [15].
- Tumor microenvironment: Mitochondrial dynamics and metabolism in stromal and immune cells within the tumor microenvironment also affect cancer progression and response to therapy [16].

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- Iatrogenically induced cancer cell differentiation: inhibiting the electron transport chain seems to decrease cancer cell growth and promote a more differentiated state of cancer cells. However, this appears to result from the reactivation of synthetic pathways that were previously suppressed by the high-energy demand associated with uncontrolled proliferation [14,17,18].

Inflammatory and Autoimmune Diseases:

- Inflammasome Activation: Damaged mitochondria release danger-associated molecular patterns (DAMPs), such as mitochondrial DNA and cardiolipin, which can activate the inflammasome and lead to the production of pro-inflammatory cytokines [19].
- Chronic Inflammation: Continued mitochondrial dysfunction and ROS production can lead to persistent inflammation, as observed in conditions like rheumatoid arthritis and inflammatory bowel disease [19,20].

1.5. Aging

Mitochondrial dysfunction plays a key role in the theory of aging. The main pathogenetic mechanisms are:

- Accumulation of damage: Over time, mitochondria accumulate damage from oxidative stress and faulty repair processes. This decreases energy production and increases ROS leakage, which accelerates cellular aging and tissue deterioration.
- Reduced Biogenesis and Dynamics: Age-related decline in mitochondrial biogenesis (formation of new mitochondria) and impaired mitochondrial dynamics (fusion and fission) further worsen dysfunction [21,22].

1.6. COVID-19

The recent COVID-19 pandemic, caused by SARS-CoV-2, further emphasizes the importance of mitochondria in disease processes. In fact, the virus proteome shows a specific preference for mitochondria. Viral proteins interact with various mitochondrial structures and functions, disrupting different activities that are essential in the development of COVID-19, including disorders affecting the brain, heart, lungs, endothelial tissue, digestive tract, kidneys, and circulation (such as shock) [20,21].

1.7. SEPSIS

All of this further underscores the potential role of mitochondria in human disease and emphasizes the need to clarify the molecular mechanisms underlying the intriguing pathogenic links between mitochondrial dysfunction and severe sepsis and septic shock, particularly in relation to prognosis and treatment [19,21,23].

In conclusion, understanding how mitochondria contribute to various diseases highlights key targets for therapeutic intervention. Strategies that aim to restore mitochondrial function, decrease oxidative stress, or modify mitochondrial dynamics offer great potential for treating these varied and challenging conditions. At the same time, due to their essential role in cell function, mitochondria are significantly impacted by various drugs, which can lead to unwanted and harmful side effects. Understanding this complex relationship is crucial for effective drug development and the improvement of treatment approaches [1–3].

For all these reasons, mitochondrial drug action is a fascinating and complex area of pharmacology, especially given the critical role of mitochondria in both normal physiology and disease states. Notably, drugs can interact with mitochondria through direct or indirect mechanisms, resulting in a variety of therapeutic or toxic effects [1–3].

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2. Mitochondria as Drug Targets

2.1. Direct Mitochondrial Targeting

This involves drugs that specifically accumulate within mitochondria or directly interact with mitochondrial components. This can be achieved through lipophilicity; in fact, many drugs, due to their lipophilic nature, can easily cross cellular membranes and the outer mitochondrial membrane. Another method involves the cationic charge; the negative membrane potential across the inner mitochondrial membrane (approximately -180 mV) attracts positively charged molecules. This is a common strategy for designing mitochondria-targeted drugs, often achieved by attaching a lipophilic cation moiety (e.g., triphenylphosphonium, TPP+) to the molecule. Additionally, some drugs might utilize existing mitochondrial transporters for uptake, although this is less common for synthetic compounds, such as DCA and BP for Monocarboxylate Transporters (MCTs); meldonium and specific CPT1/CPT2 inhibitors for the Carnitine Palmitoyltransferase System; Nucleoside Reverse Transcriptase Inhibitors (NRTIs) for nucleoside transporters [2].

Other drugs, such as Chloramphenicol, not only inhibit bacterial protein synthesis but also, due to the bacterial origin of mitochondria, can inhibit mitochondrial protein synthesis at higher doses by binding tightly and non-covalently, which affects their function [3].

Many drugs are metabolized in the liver (and other tissues) into reactive intermediates, such as epoxides, quinone imines, and free radicals, which can covalently bind to nucleophilic sites on proteins, lipids, and nucleic acids within various organelles, including mitochondria. A classic example is acetaminophen, which, in overdose cases, forms a reactive metabolite called N-acetyl-p-benzoquinone imine (NAPQI). This metabolite depletes glutathione and covalently attaches to mitochondrial proteins, leading to mitochondrial dysfunction and liver necrosis [2,24].

Also, halothane, an anesthetic, is metabolized into reactive intermediates that can covalently bind to liver mitochondrial proteins, contributing to halothane-induced hepatitis. A similar process occurs with other drugs like amiodarone, trovafloxacin, and isoniazid [2,3,25].

2.2. Indirect Mitochondrial Targeting

In cases of indirect mitochondrial targeting, drugs do not directly accumulate in mitochondria but influence mitochondrial function by modulating processes in other cellular compartments, which then affect the mitochondria. Here are some interesting examples: i. calcium dysregulation (drugs that alter intracellular calcium levels can indirectly affect mitochondrial calcium uptake and efflux, impacting mitochondrial function and integrity, such as phenylephrine, caffeine, halothane, and calcium channel blockers); ii. induction of oxidative stress (compounds that generate reactive oxygen species (ROS) in the cytoplasm can cause oxidative stress that spills over into mitochondria, damaging mitochondrial components, such as doxorubicin, cisplatin, acetaminophen, some NRTIs, and statins); iii. depletion or elevation of metabolic precursors (drugs affecting glycolysis or other cytoplasmic metabolic pathways can change the availability of substrates for mitochondrial metabolism, such as 3-Bromopyruvate, an alkylating agent targeting glycolytic enzymes like hexokinase and glyceraldehyde-3-phosphate dehydrogenase; Lonidamine, 2-Deoxyglucose (2-DG), Etomoxir, Perhexiline, inhibitors of Carnitine Palmitoyltransferase 1 (CPT1); Fasigyn (Orlistat): lipase inhibitor); iv. modulation of signaling pathways (drugs that activate or inhibit pathways such as AMPK and mTOR can indirectly influence mitochondrial biogenesis, dynamics, and function, e.g., mTOR inhibitors - Rapamycin, Everolimus -, kinase inhibitors - Sorafenib, Sunitinib -, calcium channel blockers (e.g., Verapamil, Diltiazem at high doses or in specific contexts), glucocorticoids (e.g., Dexamethasone), and, though debated, PPAR agonists (e.g., fibrates, thiazolidinediones)[2,3].

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2.3. Mechanisms of Drug-Mitochondria Interaction

2.3.1. Mitochondrial Enzyme Modulation

Mitochondria contain a wide range of enzymes essential for metabolism, including those involved in the Krebs cycle, fatty acid oxidation, amino acid metabolism, and heme synthesis. Drugs can affect these enzymes by:

i. Inhibition: Drugs like rotenone (a pesticide), certain anti-diabetic medications (e.g., metformin, though its mechanism is complex and involves other targets), fibrates, and glitazones can inhibit Complex I of the Electron Transport Chain (ETC). Krebs cycle inhibitors include fluoroacetate (a toxin) that inhibits aconitase, an enzyme in the Krebs cycle. Fatty acid oxidation inhibitors, for instance, can block enzymes such as carnitine palmitoyltransferase I (CPT1), which transports fatty acids into mitochondria. Monoamine oxidase (MAO) inhibitors, located on the outer mitochondrial membrane, break down monoamine neurotransmitters and are used as antidepressants and in Parkinson's disease treatment.

ii. Activation: Paradoxically, Pyruvate Dehydrogenase Kinase (PDK) inhibitors, such as dichloroacetate, activate pyruvate dehydrogenase by inhibiting PDK, which increases glucose oxidation in mitochondria.

iii. Allosteric Modulation: drugs can bind to an allosteric site on a mitochondrial enzyme, altering its activity without directly blocking the active site.

iv. Cofactor Interference: some drugs can disrupt the availability or use of essential cofactors for mitochondrial enzymes (e.g., vitamin deficiencies caused by drugs) [18,26–28].

2.3.2. Electron Transport Chain (ETC) Interference

The ETC consists of a series of protein complexes (Complexes I-IV) located on the inner mitochondrial membrane that generate a proton gradient. This gradient is used by ATP synthase (Complex V) to produce ATP. Disruption of the ETC is a common mechanism employed by both therapeutic and toxic agents [2,3,26].

Inhibition of Specific Complexes:

Complex I: As mentioned, drugs like rotenone, some anti-cancer agents, and some hypoglycaemic and hypolipidemic drugs [18,26]

Complex II: Malonate is a classic experimental inhibitor.

Complex III: Antimycin A is another experimental example. However, drugs can also inhibit complex III, such as Moclobemide (an antidepressant drug that mainly acts as a reversible inhibitor of monoamine oxidase (MAO), although some studies suggest it can also inhibit Complex III at higher concentrations) and Atovaquone (an antimicrobial drug used to treat parasitic infections).

Complex IV (Cytochrome c Oxidase): Cyanide and carbon monoxide are well-known potent inhibitors, leading to rapid cell death by blocking oxygen utilization. However, other drugs can also interact with COX, including disulfiram, hydrogen sulfide, nitric oxide and nitric oxide donors, some NRTIs, halothane, isoflurane, and paraquat [2,3,26–28].

Uncoupling: Uncouplers such as dinitrophenol (DNP) and FCCP, mainly used in research, dissipate the proton gradient across the inner mitochondrial membrane. This process halts ATP production and increases metabolic rate. It's important to recognize that specific molecules, such as UCPs (uncoupling proteins), have physiological roles in uncoupling [29]. Additionally, some commonly used drugs may show varying degrees of uncoupling activity, including NSAID drugs with ionizable groups (e.g., aspirin at high doses, ibuprofen, diclofenac), thyroid hormones, dicumarol, and tetracyclines [2,30,31].

ROS Generation: Certain drugs can interfere with electron flow in the ETC, leading to increased production of reactive oxygen species (ROS) at specific sites, such as Complex I or III. This leads to oxidative stress and damage to mitochondrial components. Notably, mtDNA is highly susceptible to oxidative stress because it lacks the protective histones found in nuclear DNA and has less robust repair mechanisms. Some commonly used drugs, such as metformin and phenformin, act at the level of complex I, while antimycin, myxothiazol, and atovaquone act at the level of complex III [2,18,32].

2.3.3. Drugs That Interact with or Damage mtDNA

Mitochondria contain their own circular DNA (mtDNA), which encodes 13 proteins of the ETC, two ribosomal RNAs, and 22 transfer RNAs. mtDNA is especially vulnerable to damage because of its proximity to the ETC (a significant source of ROS) and its less robust repair mechanisms compared to nuclear DNA, as previously discussed.

Many drugs can interact with or harm mitochondrial DNA (mtDNA), often causing mitochondrial dysfunction, which is an essential mechanism of drug-induced toxicity [33].

Here are some common drug classes and specific drugs known to interact with or harm mtDNA, especially:

o Nucleoside Reverse Transcriptase Inhibitors (NRTIs): This is a prominent class of antiretroviral drugs used to treat HIV infection. Drugs like zidovudine (AZT), stavudine (d4T), didanosine (ddI), and lamivudine (3TC) are nucleoside analogs that primarily target HIV reverse transcriptase. However, they can also be incorporated by mitochondrial DNA polymerase, leading to chain termination, depletion of mtDNA, and inhibition of mtDNA replication. This is a significant cause of NRTI-induced toxicities, such as myopathy, neuropathy, pancreatitis, and lipodystrophy [34].

o Chemotherapeutic Agents: many anticancer drugs target DNA replication and repair, and while primarily aimed at nuclear DNA in rapidly dividing cancer cells, they can also affect mtDNA. For example: Doxorubicin (intercalates into DNA and generates ROS, which can further damage both nuclear DNA and mtDNA. Its cardiotoxicity is partly linked to mitochondrial dysfunction and mtDNA damage); Cisplatin (forms adducts with DNA, including mtDNA, leading to replication and transcription errors. This contributes to its nephrotoxicity and ototoxicity); 5-Fluorouracil (5-FU) (a pyrimidine analog that can be misincorporated into DNA and RNA, including mitochondrial nucleic acids); Methotrexate (an antifolate that can indirectly affect mtDNA synthesis by interfering with nucleotide metabolism) [35].

o Antibiotics: such as Chloramphenicol (which inhibits mitochondrial protein synthesis in mammalian cells by binding to the 70S ribosomal subunit of bacteria and the similarly functioning 55S mitochondrial ribosome, leading to widespread effects on mitochondrial function, including issues related to mtDNA maintenance and expression); Aminoglycosides (e.g., Gentamicin, Streptomycin — which induce mitochondrial dysfunction and oxidative stress, potentially damaging mtDNA indirectly. Some evidence indicates direct interaction or disruption of mitochondrial ribosomes); Fluoroquinolones (e.g., Ciprofloxacin, Levofloxacin — which primarily target bacterial DNA gyrase and topoisomerase IV, but some studies suggest they can accumulate in mitochondria and impact mitochondrial topoisomerases or cause oxidative stress that harms mtDNA) [3,36];

o Antidepressants: Tricyclic Antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) (high doses or long-term use of certain antidepressants might cause mitochondrial dysfunction, including possible effects on mtDNA integrity, although the mechanisms are complex and less direct than NRTIs).

o Antimalarials, such as Chloroquine and Hydroxychloroquine, may accumulate in lysosomes and mitochondria, potentially affecting mitochondrial function and indirectly causing mtDNA damage through oxidative stress or interference with autophagy [37].

In conclusion, the mechanisms of mtDNA damage or interaction may include:

- Direct incorporation: as seen with NRTIs.
- Adduct formation: as with cisplatin.
- Oxidative stress: many drugs induce ROS, which then oxidize mtDNA bases (e.g., 8-oxoguanine).
- Inhibition of mtDNA replication or repair enzymes: drugs can target DNA polymerase gamma or other repair pathways.

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- Inhibition of mitochondrial protein synthesis: this can indirectly affect mtDNA stability or replication.

2.3.4. Opening of the Mitochondrial Permeability Transition Pore (MPTP)

This can cause the mitochondrial membrane to lose its integrity, leading to cell death. Importantly, there are key endogenous triggers (often mimicked by drugs) such as:

- High Matrix Ca2+ Concentration: Ca2+ overload is the most potent trigger.
- Reactive Oxygen Species (ROS) / Oxidative Stress: Increased ROS production promotes opening.
- High inorganic phosphate concentration.
- Mitochondrial Depolarization.
- ATP Depletion / ADP Depletion.

These endogenous factors are often used in laboratory settings to experimentally induce mPTP opening and study its regulation and pharmacological inhibition.

Different from that, there are well-known drugs and/or compounds capable of inducing or potentiating mPTP opening with clinical implications, first of all [38]:

- Salicylate and valproate: chemicals linked to Reye's syndrome-related hepatotoxicity, cause mitochondrial permeability transition (MPT).
- Chemotherapeutic drugs: some, such as lonidamine or arsenite compounds, are known to induce MPT, which contributes to their cell-killing effects.
- Fatty acids: specific saturated fatty acids, such as palmitate and stearate, especially in the presence of Ca2+, can induce MPT opening.
- Pro-apoptotic Bcl–2 family members: proteins like Bax and Bak are thought to participate in mPTP (Table 1)

Table 1. Potential mechanisms at the basis of Drug-Mitochondria Interactions.

Main Mechanisms at the Basis of Drug-Mitochondria Interaction	Description of Mechanisms	Drug Examples
Direct Binding to Mitochondrial Components	Drugs can directly interact with specific proteins, enzymes, or lipids within the mitochondrial membranes or matrix. This can alter their function, leading to changes in mitochondrial respiration, ATP production, or membrane potential.	Metformin, certain statins (e.g., simvastatin), some antiarrhythmic drugs (e.g., amiodarone)
Inhibition of Electron Transport Chain (ETC)	Drugs can interfere with the complexes of the ETC, blocking the flow of electrons and disrupting the proton gradient necessary for ATP synthesis. This results in reduced ATP production and increased generation of reactive oxygen species (ROS).	(Rotenone, PPARα and γ ligands inhibit Complex I), Cyanide (inhibits Complex IV), some anticancer drugs (e.g., paclitaxel)

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Uncoupling of Oxidative Phosphorylation	Uncouplers dissipate the proton gradient across the inner mitochondrial membrane, preventing ATP synthesis. Energy is released as heat instead.	Aspirin (at high doses), Dinitrophenol (DNP), certain general anesthetics
Alteration of Mitochondrial Membrane Permeability	Some drugs can increase the permeability of the mitochondrial membranes, particularly the inner membrane. This can lead to mitochondrial swelling, release of pro-apoptotic factors, and loss of membrane potential.	Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (at high doses), some anticancer drugs (e.g., doxorubicin)
Induction of Mitochondrial Oxidative Stress	Drugs can increase the production of reactive oxygen species (ROS) within mitochondria, overwhelming the antioxidant defense systems. This can lead to oxidative damage to mitochondrial DNA, proteins, and lipids, impairing mitochondrial function.	Acetaminophen (overdose), several anticancer drugs, some antiretroviral drugs
Inhibition of Mitochondrial DNA Replication/Transcription	Certain drugs can directly target mitochondrial DNA (mtDNA) or the enzymes involved in its replication and transcription, leading to depleted mtDNA or impaired synthesis of mitochondrial proteins.	Nucleoside reverse transcriptase inhibitors (NRTIs) used in HIV treatment
Modulation of Mitochondrial Dynamics (Fusion/Fission)	Drugs can alter the balance between mitochondrial fusion and fission, which are essential for maintaining mitochondrial network integrity and function. Disruptions can result in mitochondria that are either fragmented or overly fused.	Some neuroprotective agents, certain compounds affecting mitochondrial quality control
Interference with Mitochondrial Ion Homeostasis	Drugs can interfere with the transport and regulation of ions (e.g., Ca2+, K+) across mitochondrial membranes, which are essential for various mitochondrial functions, including ATP production and cell signaling.	Some calcium channel blockers, certain diuretics

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Impact on Mitochondrial Biogenesis	Some drugs can either promote or inhibit mitochondrial biogenesis. This can lead to changes in mitochondrial mass and overall cellular energy capacity.	PGC-1α activators (e.g., resveratrol), some metabolic modulators

3. The Dark Side: Drug-Induced Mitochondrial Toxicity. Some Examples of Particular Clinical Value

Many drugs, while targeting specific pathways, can unintentionally impact mitochondrial function. This aspect is often overlooked in both its pharmacological and clinical implications. Importantly, these unintended effects can lead to a variety of adverse outcomes, ranging from mild fatigue to severe organ damage. Just a few examples of clinical interest.

Many antibiotics, especially specific classes, have been found to potentially cause mitochondrial toxicity. This means they can interfere with normal mitochondrial function. Mitochondria are particularly at risk because they contain their own DNA (mtDNA) and ribosomes, which closely resemble those found in bacteria. This similarity is a vestige of the endosymbiotic theory. Since many antibiotics target bacterial ribosomes or DNA replication, they can sometimes unintentionally affect mitochondrial ribosomes or mtDNA replication in human cells.

Fluoroquinolones (e.g., Ciprofloxacin, Levofloxacin) inhibit bacterial DNA gyrase and topoisomerase IV. They can also block human mitochondrial topoisomerase II, causing mtDNA damage and disrupting mitochondrial function. Their use is linked to various side effects that may stem from mitochondrial issues, including muscle pain, tendonitis/tendon rupture, peripheral neuropathy, and CNS effects. These effects can sometimes be severe and have a lasting impact [39].

Aminoglycosides (e.g., Gentamicin, Tobramycin) target the bacterial 30S ribosomal subunit. Because of their structural similarity, they can also bind to mitochondrial 12S ribosomal RNA, inhibiting mitochondrial protein synthesis. They are known for causing ototoxicity (hearing loss, tinnitus) and nephrotoxicity (kidney damage). Ototoxicity is especially associated with mitochondrial dysfunction, particularly in individuals with specific mtDNA mutations (e.g., A1555G) that increase susceptibility [40].

Tetracyclines (e.g., Doxycycline, Minocycline) also target bacterial ribosomes (30S subunit) and can disrupt mitochondrial protein synthesis, although usually to a lesser degree than aminoglycosides. While generally well-tolerated, some mitochondrial effects have been observed in studies, but severe clinical mitochondrial toxicity is less common than with fluoroquinolones or aminoglycosides [41].

Macrolides (e.g., Azithromycin, Erythromycin) inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. They can also interact with mitochondrial ribosomes. Mitochondrial toxicity is generally considered low, but some studies have indicated potential effects, especially with prolonged use or in vulnerable individuals [42].

Linezolid (Oxazolidinone class) inhibits bacterial protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit. It is also known to inhibit mitochondrial protein synthesis in mammalian cells. Its clinical use may be associated with several adverse effects, including peripheral neuropathy, optic neuropathy, and lactic acidosis, all of which are consistent with mitochondrial dysfunction, especially with prolonged therapy (e.g., >2 weeks) [43].

Chloramphenicol: This antibiotic inhibits bacterial protein synthesis by attaching to the 50S ribosomal subunit. It is also a potent inhibitor of mitochondrial protein synthesis in mammalian cells. Known for causing bone marrow suppression (e.g., aplastic anemia), which is believed to be linked to its mitochondrial toxicity in hematopoietic cells. Due to this toxicity, its use is mainly limited to specific severe infections where other treatments are not effective [3,44]. Other classes of drugs, some of which have already been mentioned, are:

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Statins: These cholesterol-lowering drugs have been associated with muscle problems (myopathy), possibly due to their disruption of mitochondrial function and Coenzyme Q10 production, a crucial part of the ETC [45].

Anticancer Drugs: Many chemotherapeutic agents, like doxorubicin, cause cardiotoxicity by producing oxidative stress and harming mitochondria in heart cells [2,46].

Antiviral Drugs: Azidothymidine (AZT), an antiviral medication, can inhibit mitochondrial DNA replication, resulting in side effects such as myopathy [47].

Antidepressants: Some antidepressants, like amitriptyline, can cause mitochondrial toxicity by increasing oxidative stress and disrupting the mitochondrial membrane [3,48].

Antiepileptic Drugs: valproic acid, a commonly used antiepileptic, is known to cause mitochondrial toxicity, which has been linked to liver damage [49].

Non-steroidal Anti-inflammatory Drugs (NSAIDs): Some NSAIDs have been shown to interfere with oxidative phosphorylation in mitochondria [3,31].

A peculiar, intriguing, and often overlooked aspect of drug and mitochondria interaction is when this interaction influences pharmacodynamics. We also present some interesting examples of this topic.

i. Metformin's mechanism of action recently includes directly targeting mitochondria by significantly inhibiting Complex I of the electron transport chain and mitochondrial glycerophosphate dehydrogenase (mGPDH), resulting in changes in cellular energy production. This mitochondrial effect is crucial to its anti-diabetic properties. Specifically, by impairing NADH oxidation, it reduces ATP synthesis. To compensate for this energy deficit, cells increase anaerobic glycolysis, which uses more glucose and produces more lactate (yielding only two ATP molecules per glucose). A well-known risk of using metformin is lactic acidosis. There have been postmarketing cases of metformin-associated lactic acidosis, including fatal instances. However, these mitochondrial effects may also help explain metformin's potential benefits in cancer, aging, and other metabolic diseases.

Metformin also inhibits mitochondrial glycerophosphate dehydrogenase, which changes the cellular redox state and can further increase cytosolic NADH. Interestingly, the altered AMP: ATP ratio caused by mitochondrial inhibition activates AMP-activated protein kinase (AMPK), a key regulator of cellular metabolism [50,51].

ii. PPAR ligands present another interesting case. These drugs are primarily known for binding to and activating proliferative peroxisome proliferator-activated receptors, with many of their effects stemming from this interaction. These effects include hypolipidemic and/or hypoglycemic actions. However, due to their unique chemical structure, these drugs can also interact with other biological molecules, such as human hemoglobin. In fact, fibrates may function as allosteric effectors, similar to 2,3-bisphosphoglycerate, by binding to Hb both in laboratory settings and in living organisms, thus reducing the oxygen affinity of the hemoprotein. Unlike 2,3-BPG, the binding site is located at the α/α interface of the Hb tetramer [52].

More importantly, especially from a clinical perspective, is the interaction or binding with complex I of the electron transport chain (NADH: ubiquinone oxidoreductase). This binding hampers NADH oxidation at the mitochondrial level, with the extent of disruption varying depending on the PPAR class ($\gamma > \alpha$ and β). Consequently, metabolic adjustments differ. In summary, primary and partial impairment of NADH oxidation at complex I in the mitochondrial electron transport chain—caused by PPAR-alpha agonists (fibrates)—triggers cells to respond to energy deficits by increasing glycolysis. This is evidenced by increased lactate production and glucose disposal, which correlate with the degree of mitochondrial impairment. Another important compensatory mechanism appears to be a metabolic shift toward oxidative pathways in the mitochondrial respiratory chain, helping overcome the restriction caused by impaired NADH oxidation by switching to $FADH_2$ oxidation to generate energy through the still-functional components of the electron transport chain. This process likely involves the breakdown of glycerol via mitochondrial FAD-dependent glycerol-3-phosphate dehydrogenase and/or fatty acid beta-oxidation via electron-transferring flavoprotein (ETF).

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Therefore, the main metabolic adjustment stemming from NADH oxidation deficiency may be the stimulation of beta-oxidation, characterized by a NADH/$FADH_2$ synthesis ratio of roughly 1:1. This is accompanied by an inhibition of the Krebs cycle, indicated by a NADH/$FADH_2$ ratio of about 3:1. These metabolic adaptations resulting from mitochondrial dysfunction may explain several features of the pharmacotoxicological profile of various peroxisome proliferator-activated receptor (PPAR) ligands, regardless of their specific PPAR binding affinity. For PPAR-alpha ligands, especially fibrates—which are well-known hypolipidemic and hypoglycemic agents—their mechanism of action may depend on this reduction in NADH oxidation. This forces cells to meet energy needs by stimulating both glycolysis and beta-oxidation, with the latter being limited by the remaining capacity of the mitochondrial chain to carry out NADH oxidation [50,53–61]. Furthermore, the more significant hypoglycemic effect of thiazolidinediones may arise from their more potent inhibitory action on NADH oxidation exerted by these insulin sensitizers. In fact, a stronger inhibition of NADH cytochrome c reductase activity, which significantly impairs NADH oxidation, gradually hampers the compensatory mechanism via fatty acid beta-oxidation. This shift causes the cell to rely mainly on glycolysis (56-61). The suppression of fatty acid oxidation could lead to an accumulation of fatty acids, thus stimulating PPAR-gamma at the cellular level, which then enhances their own metabolism, as noted by Kersten et al. (54). This process may also account for the observed increase in adipose tissue and body weight in patients treated with these new drugs from a clinical standpoint. Additionally, the intense stimulation of glycolysis caused by mitochondrial dysfunction could explain the in vivo glucose disposal mediated by thiazolidinediones in skeletal muscles. This cannot be fully attributed to direct activation of PPAR-γ alone, given the limited presence of these receptors in muscle tissue (54, 55). From a toxicological perspective, the interactions between PPAR-alpha ligands (such as fibrates) and mitochondria could justify tissue and organ damage, as:

Myopathy and Rhabdomyolysis: These serious concerns are associated with fibrate use, especially when combined with statins, as both can impair mitochondrial function. Muscle cells, which depend heavily on energy and contain many mitochondria, are particularly vulnerable. In fact, when fibrates increase fatty acid oxidation, it can cause an imbalance if the mitochondria cannot handle this increased demand. Combined with the potential direct mitochondrial toxicity from fibrates or statins, this can lead to mitochondrial dysfunction. The outcome is decreased ATP production, muscle cell damage, and the release of substances like creatine kinase (CK) and myoglobin into the bloodstream, which are characteristic of myopathy and rhabdomyolysis [57,62,63].

Additionally, statins can lower levels of coenzyme Q10 (ubiquinone), a vital part of the electron transport chain, which further impairs mitochondrial function. The combination of increased fatty acid oxidation from fibrates and mitochondrial damage from statins creates a "perfect storm" for muscle toxicity. It explains dramatic episodes of rhabdomyolysis associated with these drugs [57].

Hepatotoxicity is also a known toxic effect of PPAR-alpha ligands. The liver, a metabolically active organ rich in mitochondria, can be damaged through increased fatty acid oxidation. This process can lead to oxidative stress and mitochondrial injury. Consequently, it may cause elevated liver enzyme levels and, in rare instances, more severe liver damage related to fibrates [56,63–67].

Unlike fibrates, PPAR-gamma ligands (also called glitazones or thiazolidinediones, such as pioglitazone and rosiglitazone) are a class of antidiabetic drugs that mainly enhance insulin sensitivity. Their primary mechanism involves activating peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor present in fat tissue, muscle, and the liver. Although their effects on lipid and glucose metabolism are complex, their interactions with mitochondria are essential and contribute to both their therapeutic benefits and some adverse effects. In fact, PPAR-gamma ligands are more potent inhibitors of complex I than PPAR-alpha, and this significant disruption of NADH oxidation worsens beta-oxidation, causing cells to rely solely on glycolysis for energy. This pharmacological action results in a strong hypoglycemic effect without reducing lipid levels [63,64,68,69]

3.1. Further Clinical Implications

Drug-induced mitochondrial dysfunction can cause various symptoms, mainly impacting organs and systems rich in mitochondria, such as muscles (myalgia, weakness), liver, kidneys, and heart. The nervous system seems to be protected, possibly because of limited permeability.

The risk of mitochondrial toxicity usually increases with higher doses and longer treatment periods.

Taking multiple drugs with mitochondrial effects, like statins and fibrates, can raise the risk.

Importantly, individuals with pre-existing mitochondrial disorders or specific genetic predispositions—such as the mtDNA A1555G mutation linked to aminoglycoside ototoxicity—are at a much higher risk, and this should be considered [70–72].

3.2. Potential Future Research

Research should continue to investigate the precise mechanisms of drug-induced mitochondrial toxicity and to identify biomarkers for early detection. The aim is to develop strategies that reduce these adverse effects and to create drugs with limited mitochondrial targeting (i.e., antibiotics that retain effectiveness against bacteria without damaging human mitochondria).

4. The Right Side: The Therapeutic Potential of Drug-Mitochondria Interaction

The vital role of mitochondria in cell physiology and pathophysiology has made them a promising target for developing new drugs. The goal of these "mitochondria-targeted therapies" is either to protect mitochondria from damage or to modify their functions for therapeutic purposes.

4.1. Potential Therapeutic Approaches Targeting Mitochondria

- Mitochondria-Targeted Antioxidants: To lessen the harmful effects of oxidative stress involved in many diseases, researchers are developing antioxidants that specifically build up in mitochondria.[12] One example is MitoQ. [73]
- Targeting Mitochondrial Apoptosis for Cancer Treatment: Since mitochondria are crucial in programmed cell death (apoptosis), drugs are being developed to specifically induce this process in cancer cells by targeting mitochondrial proteins. [70,74]
- Modulating Mitochondrial Metabolism: In diseases like obesity and diabetes, researchers are investigating drugs that can alter mitochondrial function, such as activating uncoupling proteins, but some efforts have failed due to a high occurrence of toxic effects [75].
- Repurposing Drugs: Notably, some existing drugs are being "repurposed" after discovering their beneficial effects on mitochondrial function. For example, a bile acid called UDCA, used for liver disease, has shown promise in enhancing cellular energy production in studies related to Parkinson's disease. [76].

Currently, some molecules that appear to positively affect mitochondrial function are in clinical phase studies for the pharmacological treatment of mitochondrial diseases, in particular:

- Elamipretide is a mitochondria-targeting tetrapeptide that binds to cardiolipin (CL), a lipid in the inner mitochondrial membrane. This interaction helps stabilize mitochondrial cristae structure, reduce oxidative stress, and increase adenosine triphosphate (ATP) production [77].
- Niacin, as a precursor to NAD+, is expected to increase intracellular NAD+ levels, promote mitochondrial biogenesis, and reduce symptoms of mitochondrial myopathy during the early stages of the disease [78].
- Sonlicromanol (KH176) is a small, orally available molecule designed to treat Primary Mitochondrial Diseases (PMDs). It effectively reduces abnormal cellular ROS levels, protecting OXPHOS-deficient cells from ROS-induced death. Additionally, by targeting and activating the thioredoxin/peroxiredoxin enzyme system, it helps restore redox balance. Furthermore, sonlicromanol has been shown to inhibit the microsomal PGES-1 enzyme, which contributes to its anti-inflammatory effects [79].

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- Omaveloxolone (RTA 408) activates Nrf2 and inhibits NF κB (nuclear factor kappa-light-chain-enhancer of activated B cells), leading to antioxidant and anti-inflammatory effects. Notably, multiple studies suggest that Nrf2 activation can increase mitochondrial respiration and biogenesis. Overall, the data indicate that RTA 408 may activate Nrf2 and its target genes, potentially enhancing oxidative phosphorylation, antioxidant capacity, and mitochondrial biogenesis in patients with mitochondrial myopathies [80].
- Vatiquinone inhibits the enzyme 15-lipoxygenase (15-LO), which plays an essential role in the oxidative metabolism of polyunsaturated fatty acids. This process produces lipid peroxides that contribute to oxidative stress and cell damage. By blocking 15-LO, vatiquinone reduces the generation of these harmful lipid peroxides, helping to lower oxidative stress and protect cells from injury. Additionally, vatiquinone has been shown to improve mitochondrial function [81].

5. Special Attention for Patients with Mitochondrial Diseases

Individuals with pre-existing mitochondrial diseases are especially vulnerable to the harmful effects of certain medications. For these patients, drugs generally deemed safe may substantially increase the risk of their condition worsening. Therefore, careful consideration and vigilant monitoring are crucial when prescribing medications to this group. International consensus guidelines have been put in place to help clinicians make informed decisions about safe medication use in patients with primary mitochondrial disease.[82]

6. Conclusions

In conclusion, the connection between drugs and mitochondria is an ongoing and developing area of research. Careful consideration should always be given to potential clinical implications. In fact, changes in mitochondrial function can play vital roles in pathophysiology and pharmacotoxicology, which have largely been overlooked, as recently demonstrated during the dramatic SARS-CoV-2 pandemic.

Although the risk of drug-induced mitochondrial damage remains a major concern in pharmacotherapy, increasing understanding of mitochondrial biology is opening new avenues for treatments that utilize these organelles to fight various human diseases (i.e., sepsis and cancer).

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