Review

Medication-induced mitochondrial damage and disease

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Since the first mitochondrial dysfunction was described in the 1960s, the medicine has advanced in its understanding the role mitochondria play in health and disease. Damage to mitochondria is now understood to play a role in the pathogenesis of a wide range of seemingly unrelated disorders such as schizophrenia, bipolar disease, dementia, Alzheimer's disease, epilepsy, migraine headaches, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia, retinitis pigmentosa, diabetes, hepatitis C, and primary biliary cirrhosis. Medications have now emerged as a major cause of mitochondrial damage, which may explain many adverse effects. All classes of psychotropic drugs have been documented to damage mitochondria, as have stain medications, analgesics such as acetaminophen, and many others. While targeted nutrient therapies using antioxidants or their precursors (e.g., N-acetyl-cysteine) hold promise for improving mitochondrial function, there are large gaps in our knowledge. The most rational approach is to understand the mechanisms underlying mitochondrial damage for specific medications and attempt to counteract their deleterious effects with nutritional therapies. This article reviews our basic understanding of how mitochondria function and how medications damage mitochondria to create their occasionally fatal adverse effects.

Keywords: Antioxidant / Coenzyme Q10 / L-carnitine / Lipoic acid / Mitochondria

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1 Introduction

Mitochondria are the powerhouses of our cells. They are responsible for generating energy as adenosine triphosphate (ATP) and heat, and are involved in the apoptosis-signaling pathway. Current theory holds that mitochondria are the descendants of aerobic bacteria that colonized an ancient prokaryote between 1 and 3 billion years ago [1–3]. This allowed for the evolution of the first eukaryotic cell capable of aerobic respiration, a necessary precursor to the evolution of multicellular organisms [1]. Supporting this theory is the observation that mitochondria are the only other subcellular structure aside from the nucleus to contain DNA. However, unlike nuclear DNA (nDNA), mitochondrial DNA (mtDNA) are not protected by histones [4]. nDNA wraps around histones, which then physically shield the DNA from damaging free radicals [5] and are also required to repair dsDNA breaks [6]. Since mtDNA lacks the structural protection of histones and their repair mechanisms, they are quite susceptible to damage.

The first mitochondrial disease was described by Luft et al. in 1962 [7], when a euthyroid 35-year-old female presented with myopathy, excessive perspiration, heat intolerance, polydipsia with polyuria, and a basal metabolic rate 180% of normal. The patient suffered from an uncoupling of oxidative phosphorylation (ox-phos). Ox-phos is the major cellular energy-producing pathway. Energy, in the form of ATP, is produced in the mitochondria through a series of reactions in which electrons liberated from the reducing substrates nicotine adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH) are delivered to O₂ via a chain of respiratory proton (H⁺) pumps [8]. The uncoupling of ox-phos leads to the generation of heat without generating ATP, which was the dysfunction underlying this...
symptoms such as fatigue, muscle pain, shortness of breath, and abdominal pain can easily be misdiagnosed as collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness [29].

Since this first documented case, mitochondrial dysfunction has been implicated in nearly all pathologic and toxicologic conditions [9] (these conditions are outlined in Tables 1 and 2). The conditions include sarcopenia and nonalcoholic steatohepatitis; acquired diseases such as diabetes and atherosclerosis; neurodegenerative diseases such as Parkinson's and Alzheimer's diseases; and inherited diseases, collectively called mitochondrial cytopathies.

However, since symptoms vary from case to case, age of onset, and rate of progression, mitochondrial dysfunction can be difficult to diagnose when it first appears. According to BH Cohen, who wrote a July 2001 article in the Cleveland Clinic Journal of Medicine, “The early phase can be mild and may not resemble any known mitochondrial disease. In addition, symptoms such as fatigue, muscle pain, shortness of breath, and abdominal pain can easily be mistaken for collagen vascular disease, chronic fatigue syndrome, fibromyalgia, or psychosomatic illness” [29].

Patient's presentation. To compensate, her mitochondria enlarged and multiplied, which was evident in a histological examination of muscle biopsies.

Mitochondria produce more than 90% of our cellular energy by ox-phos [33]. Energy production is the result of two closely coordinated metabolic processes – the tricarboxylic acid (TCA) cycle, also known as the Krebs or citric acid cycle, and the electron transport chain (ETC). The TCA cycle converts carbohydrates and fats into some ATP, but its major job is the capture of electrons by the coenzymes NADH and FADH which shuttle this energy to the ETC.

The overall pathway for the TCA cycle is as follows: catabolism of glucose in the cytosol produces two molecules of pyruvate, which pass through the mitochondrial's double membrane to enter the TCA cycle. As the pyruvate molecules pass through the membranes, they encounter two enzymes, pyruvate carboxylase and pyruvate dehydrogenase (PDH). Although PDH is referred to as one enzyme, it is actually a complex of three separate enzymes – PDH, dihydrolipoyl transacetylase, and dihydrolipoyl dehydrogenase. The PDH complex requires a variety of coenzymes and substrates for its function – coenzyme A (CoA), which is derived from pantothenic acid (vitamin B5); NAD+, which contains niacin (vitamin B3); FAD+, which contains riboflavin (vitamin B2); lipoic acid; and thiamin pyrophosphate (TPP), which, as the name indicates, contains thiamin (vitamin B1).

When there is ample energy (relatively high concentrations of ATP), pyruvate carboxylase is activated and shut-

### Table 1. Signs, symptoms and diseases associated with mitochondrial dysfunction [29]

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Possible symptom or disease</th>
</tr>
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<tbody>
<tr>
<td>Muscles</td>
<td>Hypotonia, weakness, cramping, muscle pain, ptosis, ophthalmoplegia</td>
</tr>
<tr>
<td>Brain</td>
<td>Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke, and stroke-like events</td>
</tr>
<tr>
<td>Nerves</td>
<td>Neuropathic pain and weakness (which may be intermittent), acute and chronic inflammatory demyelinating polyneuropathy, absent deep tendon reflexes, neuropathic gastrointestinal problems (gastroesophageal reflux, constipation, bowel pseudo-obstruction), fainting, absent or excessive sweating, aberrant temperature regulation</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Proximal renal tubular dysfunction (Fanconi syndrome); possible loss of protein (amino acids), magnesium, phosphorus, calcium, and other electrolytes</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiac conduction defects (heart blocks), cardiomyopathy</td>
</tr>
<tr>
<td>Liver</td>
<td>Hypoglycemia, gluconeogenic defects, nonalcoholic liver failure</td>
</tr>
<tr>
<td>Eyes</td>
<td>Optic neuropathy and retinitis pigmentosa</td>
</tr>
<tr>
<td>Ears</td>
<td>Sensorineural hearing loss, aminoglycoside sensitivity</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Diabetes and exocrine pancreatic failure</td>
</tr>
<tr>
<td>Systemic</td>
<td>Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger</td>
</tr>
</tbody>
</table>

### Table 2. Acquired conditions in which mitochondrial dysfunction has been implicated

- Diabetes [3, 10, 11]
- Huntington's disease [12]
- Cancer [3], including hepatitis-C virus-associated hepatocarcinogenesis [13]
- Alzheimer disease [12]
- Parkinson's disease [12]
- Bipolar disorder [14, 15]
- Schizophrenia [15]
- Aging and senescence [3, 16 – 19]
- Anxiety disorders [20]
- Nonalcoholic steatohepatitis [21]
- Cardiovascular disease [10], including atherosclerosis [22]
- Sarcopenia [23]
- Exercise intolerance [24]
- Fatigue, including chronic fatigue syndrome [25, 26], fibromyalgia [27, 28], and myofascial pain [28]
Table 3. Inherited conditions in which mitochondrial dysfunction has been implicated [29]

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Kearns–Sayre syndrome (KSS)</td>
<td>external ophthalmoplegia, cardiac conduction defects, and sensorineural hearing loss</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy (LHON)</td>
<td>visual loss in young adulthood</td>
</tr>
<tr>
<td>Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS)</td>
<td>varying degrees of cognitive impairment and dementia, lactic acidosis, strokes, and transient ischemic attacks</td>
</tr>
<tr>
<td>Myoclonic epilepsy and ragged-red fibers (MERRF)</td>
<td>progressive myoclonic epilepsy, clumps of diseased mitochondria accumulate in the subsarcolemmal region of the muscle fiber</td>
</tr>
<tr>
<td>Leigh syndrome subacute sclerosing encephalopathy</td>
<td>seizures, altered states of consciousness, dementia, ventilatory failure</td>
</tr>
<tr>
<td>Neuropathy, ataxia, retinitis pigmentosa, and ptosis (NARP)</td>
<td>dementia, in addition to the symptoms described in the acronym</td>
</tr>
<tr>
<td>Myoneurogenic gastrointestinal encephalopathy (MNGIE)</td>
<td>gastrointestinal pseud-obstruction, neuropathy</td>
</tr>
</tbody>
</table>

Delivered to diatomic oxygen (O2) complexes, passing down an electrochemical gradient to be donated from NADH and FADH flow through the ETC by the combination of nDNA and mtDNA [35]. Electrons nDNA, the other respiratory chain complexes are encoded both nDNA and mtDNA. Complex II is entirely encoded by mtDNA. Production of mitochondrial respiratory complexes require consists of a series of five enzyme complexes, designated I–V. Embedded in the inner mitochondrial membrane and connected to the TCA cycle.

Production of mitochondrial respiratory complexes require a series of five enzyme complexes, designated I–V. Embedded in the inner mitochondrial membrane and connected to the TCA cycle. These complexes are encoded by both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Complex II is entirely encoded by mtDNA. Production of mitochondrial respiratory complexes require a series of five enzyme complexes, designated I–V. Embedded in the inner mitochondrial membrane and connected to the TCA cycle.

Mitochondrial DNA encodes the complete set of genes necessary for mitochondrial respiration, including the subunit genes of the respiratory chain complexes. The complex II (succinate dehydrogenase) is entirely encoded by mtDNA. The other respiratory chain complexes are encoded by both nDNA and mtDNA. Complexes I, III, and IV contain flavins, which contain riboflavin, iron–sulfur clusters, copper, or iron-containing heme moieties.

Ubiquinone shuttles electrons from complexes I and II to complex III. Cytochrome c, an iron-containing heme protein with a binuclear center of a copper ion [36], transfers electrons from complex III to IV. During this process, protons are pumped through the inner mitochondrial membrane to the intermembrane space to establish a proton motive force, which is used by complex V to phosphorylate adenosine diphosphate (ADP) to ATP. Proper functioning of the TCA cycle and ETC require all the nutrients involved in the production of enzymes and all the cofactors needed to activate the enzymes.

3 Mechanisms of mitochondria-induced injury

Damage to mitochondria is caused primarily by reactive oxygen species (ROS) generated by the mitochondria themselves [37, 38]. It is currently believed that the majority of ROS are generated by complexes I and III [39], likely due to the release of electrons by NADH and FADH into the ETC. Mitochondria consume approximately 85% of the oxygen utilized by the cell during its production of ATP [40]. During normal ox-phos, 0.4–4.0% of all oxygen consumed is converted in mitochondria to the superoxide (O2•−) radical [40–42]. Superoxide is transformed to hydrogen peroxide (H2O2) by the detoxification enzymes manganese superoxide dismutase (MnSOD) or copper/zinc superoxide dismutase (Cu/ Zn SOD) [3], and then to water by glutathione peroxidase (GPX) or peroxiredoxin III (PRX III) [43]. However, when these enzymes cannot convert ROS such as the superoxide radical to H2O fast enough oxidative damage occurs and accumulates in the mitochondria [44, 45]. Glutathione in GPX is one of the body’s major antioxidants. Glutathione is a tripeptide containing glutamine, glycine, and cysteine, and GPX requires selenium as a cofactor.

Superoxide has been shown in vitro to damage the iron–sulfur cluster that resides in the active site of aconitate, an enzyme in the TCA cycle [46]. This exposes iron, which...
Table 4. Key nutrients required for proper mitochondrial function [9, 60]

<table>
<thead>
<tr>
<th>Required for the TCA cycle</th>
<th>Required for PDH complex</th>
<th>Required for ETC complexes Required for shuttling electrons between ETC complexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) Iron, sulfur, thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), cysteine, magnesium, manganese, and lipoic acid.</td>
<td>(i) Ubiquinone (CoQ10), riboflavin, iron, sulfur, copper</td>
<td>(ii) Ubiquinone, copper, iron</td>
</tr>
<tr>
<td>(ii) Synthesis of heme for heme-dependent enzymes in the TCA cycle require several nutrients, including iron, copper, zinc, riboflavin, and pyridoxine (vitamin B6) [60].</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iii) Synthesis of l-carnitine requires ascorbic acid (vitamin C). Riboflavin, niacin, thiamin, pantothenic acid, and lipoic acid.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mitochondria are particularly vulnerable to free radicals include lipids, proteins, ox-phos enzymes, and mtDNA [40, 47]. Direct damage to mitochondrial proteins decreases their affinity for substrates or coenzymes and, thereby, decrease their function [48]. Compounding the problem, once a mitochondrion is damaged, mitochondrial function can be further compromised by increasing the cellular requirements for energy repair processes [9]. Mitochondrial dysfunction can result in a feed-forward process, whereby mitochondrial damage causes additional damage.

Complex I is especially susceptible to NO damage, and animals administered natural and synthetic complex I antagonists have undergone death of neurons [49–51]. Complex I dysfunction has been associated with Leber hereditary optic neuropathy, Parkinson's disease, and other neurodegenerative conditions [52, 53].

As a medical concern, hyperglycemia induces mitochondrial superoxide production by endothelial cells, which is an important mediator of diabetic complications such as cardiovascular disease [43, 54]. Endothelial superoxide production also contributes to atherosclerosis, hypertension, heart failure, aging, sepsis, ischemia-reperfusion injury, and hypercholesterolemia [55].

Inflammatory mediators such as tumor necrosis factor alpha (TNF-α) have been associated in vitro with mitochondrial dysfunction and increased ROS generation [56].

In a model for congestive heart failure (CHF), application of TNF to cultured cardiac myocytes increased ROS generation and myocyte hypertrophy [57]. TNF results in mitochondrial dysfunction by reducing complex III activity in the ETC, increasing ROS production, and causing damage to mtDNA [58].

Metabolic dysregulation can also cause mitochondrial dysfunction. Vitamins, minerals, and other metabolites act as necessary cofactors for the synthesis and function of mitochondrial enzymes and other compounds that support mitochondrial function (see Table 4), and diets deficient in micronutrients can accelerate mitochondrial decay and contribute to neurodegeneration [59]. For example, enzymes in the pathway for heme synthesis require adequate amounts of pyridoxine, iron, copper, zinc, and riboflavin [60]. Deficiencies of any component of the TCA cycle or ETC can lead to increased production of free radicals and mtDNA damage. For example, low iron status decreases mitochondrial activity by causing a loss of complex IV and increasing oxidative stress [61].

4 Medication-induced mitochondrial damage

Mitochondrial dysfunction is increasingly implicated in the etiology of drug-induced toxicities, but mitochondrial toxicity testing is still not required by the US FDA for drug approval [62]. Mitochondria can be damaged both directly and indirectly by medications (Table 5). Medications can directly inhibit mtDNA transcription of ETC complexes, damage through other mechanisms ETC components, and inhibit enzymes required for any of the steps of glycolysis and β-oxidation. Indirectly, medications may damage mitochondrial via the production of free radicals, by decreasing endogenous antioxidants such as glutathione and by depleting the body of nutrients required for the creation or proper function of mitochondrial enzymes or ETC complexes. Damage to mitochondria may explain the side effects of many medications.

Barbiturates were the first drugs noted in vitro to inhibit mitochondrial respiration by inhibiting NADH dehydrogenase, which is situated at complex I of the ETC [63]. This same mechanism also explains how rotenone caused mitochondrial damage, thereby making it a useful drug inducing and studying Parkinson's disease-like symptoms in animal models [63]. Drugs and some endogenous compounds can sequester CoA (aspirin, valproic acid), inhibit mitochondrial β-oxidation enzymes (tetracyclines, several 2-arylpropionate anti-inflammatory drugs, aminoptine, and tianeptine), or inhibit both mitochondrial β-oxidation and oxphos (endogenous bile acids, amiodarone, perhexiline, and
Table 5. Medications documented to induce mitochondrial damage [10, 35, 63–90]

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism medications</td>
<td>Disulfiram (Antabuse®)</td>
</tr>
<tr>
<td>Analgesic (for pain) and anti-inflammatory</td>
<td>Aspirin, acetaminophen (Tylenol), diclofenac (Voltaren®), Voltarol®, Diclon®, Dicloflex®</td>
</tr>
<tr>
<td></td>
<td>Difen and Catiflam®, fenopreno (Nalfon®), indomethacin (Indocin®, Indocid®, Indochron E-R®, Indocin-SR®), Naproxen (Aleve®, Naprosyn®)</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Bupivacaine, lidocaine, propofol</td>
</tr>
<tr>
<td>Angina medications</td>
<td>Perhexiline, amiodarone (Cordaron®), Diethylaminoethoxyhexestrol (DEAEH)</td>
</tr>
<tr>
<td>Antiarrhythmic (regulates heartbeat)</td>
<td>Amiodarone (Cordaron®)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Tetracycline, antilmycin A</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline (Lentizol®), amoxapine (Asendis®), citalopram (Cipramil®), fluoxetine (Prozac, Symbyax, Sarafem, Fontex, Fontexin, Ladosse, Flucin, Prodep, Fludac, Oxetin, Seronil, Lorvan)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine</td>
</tr>
<tr>
<td>Anxiety medications</td>
<td>Alprazolam (Xanax®), diazepam (valium, diastat)</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Amobarbital (Amytal®), aprobarbital, butabarbital, butalbital (Fiorinal®, hexobarbital (Sombulex®), methylphenobarbital (Mebaral®), pentobarbital (Nembutal®), phenobarbital (Luminal®), primidone, propofol, secobarbital (Seconal®), Talbutal®, thiobarbital</td>
</tr>
<tr>
<td>Cholesterol medications</td>
<td>Statins – atorvastatin (Lipitor®), Torvasst®, fluvasstatin (Lescol®), lovastatin (Mevacor®, Altocor®), pitavastatin (Livalo®, Pitava®), pravastatin (Pravachol®, Selectline®, Lipostat®), rosuvastatin (Crestor®), simvastatin (Zocor®, Lipex®) bile acids – cholestyramine (Ques-tran®), clofibrate (Atrmidis®), ciprofibrate (Modalam®), colestipol (Colestid®), colesvelam (Welchol®)</td>
</tr>
<tr>
<td>Cancer (chemotherapy) medications</td>
<td>Mitomycin C, proflromycin, adriamycin (also called doxorubicin and hydroxydaunorubicin and included in the following chemotherapeutic regimens – ABVD, CHOP, and FAC)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Tarcine (Cognex®), Galantamine (Reminyl®)</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td>Metformin (Fortamet®, Glucophage®, Glucophage XR, Riomet®), troglitazone, rosiglitazone, buformin</td>
</tr>
<tr>
<td>HIV/AIDS medications</td>
<td>Atipiaλ, Combivir®, Emtriva®, Epivi® (abacavir sulfate), Epzicomb, Hivid® (ddC, zalcitabine), Retrovir® (AZT, ZDV, zidovudine), Trizivir®, Truvada®, Atripla® (3TC), stavudine (d4T, stavudine), Zidovudine (ddI, didanosine), Videx® (ddI, didanosine), Lipex® (ddC, zalcitabine), Symbyax, Depakene syrup, Depakene, depakate ER, depakate sprinkle, divalprox sodium)</td>
</tr>
<tr>
<td>Epilepsy/Seizure medications</td>
<td>Valproic acid (Depacon®, Depakene®, Depakene syrup, Depakote®, depakate ER, depakate sprinkle, divalprox sodium)</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
</tr>
<tr>
<td>Parkinson’s disease medications</td>
<td>Tolcapone (Tasmar®, Entacapone (COMTan® also in the combination drug Stalevo®))</td>
</tr>
</tbody>
</table>

Diethylaminoethoxyhexestrol) [64]. Other substances impair mitochondrial function such as INF-alpha (INF-α) or mtDNA transcription (dideoxynucleosides) [64]. In severe cases, impairment of energy production may contribute to liver failure, coma, and death [64].

Many psychotropic medications also damage mitochondrial function. These include antidepressants (amitriptyline (Lentizol®), amoxapine (Asendis®), citalopram (Cipramil®), fluoxetine (Prozac, Symbyax, Sarafem, Fontex, Fontexin, Ladosse, Flucin, Prodep, Fludac, Oxetin, Seronil, Lorvan)), antipsychotics (chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine), dementia medications (galantamine (Reminyl®)), tacrine (Cognex®), seizure medications (valproic acid (Depacon®, Depakene®, depakene syrup, Depakote®, depa-kate ER, depakate sprinkle, divalprox sodium)), mood stabilizers such as lithium, and Parkinson’s disease medications such as tolcapone (Tasmar®, entacapone (COMTan® also in the combination drug Stalevo®)) and benzodiazepines (Diazepam®, Alprazolam®) [63–73, 91, 92].

Adverse effects of the nucleoside reverse transcriptase inhibitor (NRTI) class of medications, including zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), and abacavir (ABC), result from decreased mitochondrial energy-generating capacity [35]. The underlying mechanism for this is via the inhibition of DNA polymerase-γ, the only enzyme responsible for mtDNA replication [74]. Inhibiting polymerase-γ can lead to a decrease in mtDNA, the 13 subunits of the mitochondrial ox-phos system and cellular energy production [35, 74]. NRTI-induced mitochondrial dysfunction explains many adverse reactions caused by these medications including polyneuropathy, myopathy, cardiomyopathy, steatosis, lactic acidosis, pancreatitis, pancytopenia, and proximal renal tubule dysfunction [74].

Acetaminophen (paracetamol, N-acetyl-p-aminophenol), the active ingredient in Tylenol® and more than 100 different products, is the leading cause of drug-induced liver failure in the US [93]. Each year more than 450 deaths are caused by acute and chronic acetaminophen toxicity [93]. Acetaminophen is metabolized in the liver primarily by the cytochrome P450 (CYP) isoenzyme CYP2E1 [94]. When acetaminophen passes through the CYP2E1 enzyme it is metabolized to N-acetyl-p-benzoquinone-imine...
(NAPQI), a toxic intermediate that is subsequently reduced and conjugated with glutathione before the final substrate is excreted in the urine [94]. Therefore, the earliest effect of acetaminophen metabolism is a depletion of hepatic glutathione, the accumulation of free radicals, and decreased mitochondrial respiration [95]. Since glutathione depletion is a mechanism by which acetaminophen causes hepatocellular necrosis, it is not surprising that the antidote for acetaminophen poisoning is N-acetylcysteine (NAC), which increases glutathione [96, 97].

Mechanisms of mitochondrial damage and tissues affected differ between medications. For example, valproic acid depletes carnitine [75] and decreases β-oxidation in the liver [64], thereby contributing to steatosis [64]. The antipsychotic medications chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, and olanzapine inhibit ETC function [63, 65–68]. The anxiety mediation Diazepam® was shown to inhibit mitochondrial function in rat brain, while Alprazolam® does so in the liver [73, 92].

5 Conclusions

Since the first mitochondrial dysfunction was described in the 1960s, the central role mitochondria play in health and disease has been widely documented. Mitochondrial damage is now understood to play a role in a wide range of seemingly unrelated disorders such as schizophrenia, diabetes, Parkinson’s disease, chronic fatigue syndrome, and nonalcoholic steatohepatitis. Recently it has become known that iatrogenic mitochondrial explains many adverse reactions from medications. Mitochondrial toxicity testing as part of the preapproval process for medications may help protect the public by identifying the most toxic medications before they are allowed to reach the market. By understanding the mechanisms underlying drug-induced mitochondrial damage, it may be possible to develop nutritional strategies to decrease the potentially toxic effects of medications. While targeted nutrient therapies using antioxidants or their precursors (e.g., N-acetylcysteine) hold promise for improving mitochondrial function, there are large gaps in our knowledge. The most rational approach is to understand the mechanisms underlying mitochondrial damage for specific medications, and attempt to counteract their deleterious effects with nutritional therapies. While randomized, controlled trials are lacking in this regard, they hopefully will be designed and conducted in coming years so that clinicians will have a clearer understanding of how to best protect and treat their patients.

The authors have declared no conflict of interest.

6 References


