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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 prescursors (*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. 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 and *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 O_2 *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

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Abbreviations: ATP, adenosine triphosphate; **CoA,** coenzyme A; **ETC,** electron transport chain; **FADH,** flavin adenine dinucleotide; **GPX,** glutathione peroxidase; **mtDNA,** mitochondrial DNA; **NADH,** nicotine adenine dinucleotide; **nDNA**, nuclear DNA; **NO,** nitric oxide; **ox-phos,** oxidative phosphorylation; **PDH,** pyruvate dehydrogenase; **ROS,** reactive oxygen species; **TCA,** tricarboxylic acid; **TNF-α**, tumor necrosis factor alpha

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

Organ system	Possible symptom or disease
Muscles	Hypotonia, weakness, cramping, muscle pain, ptosis, opthalmoplegia
Brain	Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke, and stroke-like events
Nerves	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
Kidneys	Proximal renal tubular dysfunction (Fanconi syndrome); possible loss of protein (amino acids), magnesium, phosphorus, calcium, and other electrolytes
Heart	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia, gluconeogenic defects, nonalcoholic liver failure
Eyes	Optic neuropathy and retinitis pigmentosa
Ears	Sensorineural hearing loss, aminoglycoside sensitivity
Pancreas	Diabetes and exocrine pancreatic failure
Systemic	Failure to gain weight, short stature, fatigue, respiratory problems including intermittent air hunger.

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]

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

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 – 3). 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].

2 Mitochondria structure and function

Cellular energy requirements control how many mitochondria are in each cell. A single somatic cell can contain from 200 to 2000 mitochondria [30, 31], while human germ cells such as spermatozoa contain a fixed number of 16 mitochondria and oocytes have up to 100 000 [32]. The largest number of mitochondria are found in the most metabolically active cells, such as skeletal and cardiac muscle and the liver and brain. Mitochondria are found in every human cell except mature erythrocytes [29].

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 mitochondrion'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 3. Inherited conditions in which mitochondrial dysfunction has been implicated [29]

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

tles the pyruvates in the direction of gluconeogenesis. When energy demands are high (relatively low concentration of ATP), the two pyruvate molecules pass through the PDH complex to produce two molecules of acetyl CoA, which enter the TCA cycle. There are nine intermediates in the TCA cycle. To pass through this cycle completely, the enzymes catalyzing the biotransformation of the intermediates require the following cofactors: cysteine, iron, niacin, magnesium, manganese, thiamin, riboflavin, pantothenic acid, and lipoic acid [34]. Once the two molecules of acetyl CoA are produced, each acetyl CoA produces three molecules of NADH and two molecules of FADH, for a total of six NADH and four FADH *per* one molecule of pyruvate. Additionally, acetyl CoA can be produced by oxidation of fatty acids, which then requires the nutrient L-carnitine to shuttle the acetyl CoA into the mitochondria to enter the TCA cycle.

NADH and FADH carry electrons to the ETC, which is embedded in the inner mitochondrial membrane and consists of a series of five enzyme complexes, designated I–V. Production of mitochondrial respiratory complexes require both nDNA and mtDNA. Complex II is entirely encoded by nDNA, the other respiratory chain complexes are encoded by the combination of nDNA and mtDNA [35]. Electrons donated from NADH and FADH flow through the ETC complexes, passing down an electrochemical gradient to be delivered to diatomic oxygen (O_2) *via* a chain of respiratory proton (H^+) pumps [8].

Complexes I–IV involve ubiquinone (Coenzyme Q10, abbreviated as CoQ10). Complex I is NADH dehydrogenase or NADH/ubiquinone oxidoreductase; complex II is succinate dehydrogenase (SDH) or succinate/ubiquinone oxidoreductase; complex III is the bc1 complex or ubiquinone/cytochrome *c* oxidoreductase; complex IV is cytochrome *c* oxidase (COX) or reduced cytochrome *c*/oxygen oxidoreductase; and complex V is ATP synthase or proton-translocating ATP synthase [3]. Complexes I–IV contain flavins, which contain riboflavin, iron–sulfur clusters, copper centers, 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) by ATP synthase, thereby creating 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 (O_2^-) radical [40–42]. Superoxide is transformed to hydrogen peroxide (H_2O_2) 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 peroxidredoxin III (PRX III) [43]. However, when these enzymes cannot convert ROS such as the superoxide radical to H_2O 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 aconitase, an enzyme in the TCA cycle [46]. This exposes iron, which

Table 4. Key nutrients required for proper mitochondrial function [9, 60]

Required for the TCA cycle	(i) Iron, sulfur, thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), cysteine, magnesium, manganese, and lipoic acid. (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]. (iii) Synthesis of L-carnitine requires ascorbic acid (vitamin C).
Required for PDH complex	Riboflavin, niacin, thiamin, pantothenic acid, and lipoic acid
Required for ETC complexes	Ubiquinone (CoQ10), riboflavin, iron, sulfur, copper
Required for shuttling electrons between ETC complexes	Ubiquinone, copper, iron

reacts with H_2O_2 to produce hydroxyl radicals by way of a Fenton reaction [46]. Additionally, nitric oxide (NO) is produced within the mitochondria by mitochondrial NO synthase (mtNOS) [42], and also freely diffuses into the mitochondria from the cytosol [43]. NO reacts with O_2^- to produce another radical, peroxynitrite ($ONOO^-$) [43]. Together, these two radicals as well as others can do great damage to mitochondria and other cellular components.

Within the mitochondria, elements that 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.

Barbituates 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, amineptine, and tianeptine), or inhibit both mitochondrial β-oxidation and ox-phos (endogenous bile acids, amiodarone, perhexiline, and

Table 5. Medications documented to induce mitochondrial damage [10, 35, 63 – 90]

Drug class	Drugs
Alcoholism medications	Disulfiram (Antabuse®)
Analgesic (for pain) and anti-inflammatory	Aspirin, acetaminophen (Tylenol), diclofenac (Voltaren®, Voltarol®, Diclon®, Dicloflex® Difen and Cataflam®), fenoprofen (Nalfon®), indomethacin (Indocin®, Indocid®, Indochron E-R® Indocin-SR®), Naproxen (Aleve®, Naprosyn®)
Anesthetics	Bupivacaine, lidocaine, propofol
Angina medications	Perhexiline, amiodarone (Cordarone®), Diethylaminoethoxyhexesterol (DEAEH)
Antiarrhythmic (regulates heartbeat)	Amiodarone (Cordarone)
Antibiotics	Tetracycline, antimycin A
Antidepressants	Amitriptyline (Lentizol), amoxapine (Asendis), citalopram (Cipramil), fluoxetine (Prozac, Symbyax, Sarafem, Fontex, Foxetin, Ladose, Fluctin, Prodep, Fludac, Oxetin, Seronil, Lovan)
Antipsychotics	Chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine
Anxiety medications	Alprazolam (Xanax®), diazepam (valium, diastat)
Barbiturates	Amobarbital (Amytal®), aprobarbital, butabarbital, butalbital (Fiorinal®, hexobarbital (Sombulex®), methylphenobarbital (Mebaral®), pentobarbital (Nembutal®), phenobarbital (Luminal®), primidone, propofol, secobarbital (Seconal®), Talbutal®), thiobarbital
Cholesterol medications	Statins – atorvastatin (Lipitor®, Torvast®), fluvastatin (Lescol®), lovastatin (Mevacor®, Altocor®), pitavastatin (Livalo®, Pitava®), pravastatin (Pravachol®, Selektine®, Lipostat®), rosuvastatin (Crestor®), simvastatin (Zocor®, Lipex®) bile acids – cholestyramine (Questran®), clofibrate (Atromid-S®), ciprofibrate (Modalim®), colestipol (Colestid®), colesevelam (Welchol®)
Cancer (chemotherapy) medications	Mitomycin C, profiromycin, adriamycin (also called doxorubicin and hydroxydaunorubicin and included in the following chemotherapeutic regimens – ABVD, CHOP, and FAC)
Dementia	Tacrine (Cognex®),Galantamine (Reminyl®)
Diabetes medications	Metformin (Fortamet®, Glucophage®, Glucophage XR, Riomet [1]), troglitazone, rosiglitazone, buformin
HIV/AIDS medications	AtriplaÔ, Combivir®, Emtriva®, Epivir® (abacavir sulfate), EpzicomÔ, Hivid® (ddC, zalcitabine), Retrovir® (AZT, ZDV, zidovudine), Trizivir®, Truvada®, Videx® (ddI, didanosine), Videx® EC, Viread®, Zerit® (d4T, stavudine), Ziagen®, Racivir®
Epilepsy/Seizure medications	Valproic acid (Depacon®, Depakene®, Depakene syrup, Depakote®, depakote ER, depakote sprinkle, divalproex sodium)
Mood stabilizers	Lithium
Parkinson's disease medications	Tolcapone (Tasmar®, Entacapone (COMTan®, also in the combination drug Stalevo®)

diethylaminoethoxyhexestrol) [64]. Other substances impair mtDNA transcription such as INF-alpha (INF-α) or mtDNA replication (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®, Foxetin®, Ladose®, Fluctin®, Prodep®, Fludac®, Oxetin®, Seronil®, Lovan®)), antipsychotics (chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine), dementia medications (galantamine (Reminyl®), tacrine (Cognex®)), seizure medications (valproic acid (Depacon®, Depakene®, depakene syrup, Depakote®, depakote ER, depakote sprinkle, divalproex 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 dsyfuntion [74].

Acetaminophen (paracetamol, *N*-acetyl-*p*-amino-phenol), 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 prescursors (*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.

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