The interactions of some commonly consumed drugs with mitochondrial adaptations to exercise

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Robinson MM, Hamilton KL, Miller BF. The interactions of some commonly consumed drugs with mitochondrial adaptations to exercise. J Appl Physiol 107: 8–16, 2009. First published May 7, 2009; doi:10.1152/japplphysiol.00343.2009.—The importance of mitochondrial dysfunctions in the progression of chronic disease has been well established. Patients with chronic diseases are often prescribed a variety of medications, many of which have been shown to induce mitochondrial dysfunction. Exercise is a known stimulus for mitochondrial biogenesis and also recommended to patients as a lifestyle modification to supplement drug therapy. However, the potential interference of those drugs with mitochondrial adaptations to exercise has not been thoroughly investigated. This review provides a summary and discussion of known and potential interactions of commonly consumed drugs with exercise-induced mitochondrial adaptations.

β-adrenergic blockers; nonsteroidal anti-inflammatory drug; statins; mitochondrial biogenesis; chronic disease

CHRONIC DISEASES ARE THE LEADING killers in the United States. Current health recommendations encourage physical activity and prevention and treatment for chronic disease (20). In addition, patients with chronic disease are often prescribed a variety of drugs in an attempt to reduce the progression of disease or to alleviate symptoms of the disease. While these patients are frequently encouraged to engage in routine physical activity, the interaction between exercise and drugs, both prescription and nonprescription, is not well known. Thus patients may be inadvertently attenuating potential adaptations to exercise that could otherwise be beneficial.

It is now apparent that mitochondrial dysfunction is causal in many disease states (51, 63), and that improvement in mitochondrial function could be an important therapeutic target. It has been demonstrated that mitochondrial dysfunction is associated with obesity (28), insulin resistance (46), heart disease (10), and aging (61). Endurance exercise is associated with increased mitochondrial size, number, and function, and this improvement is thought to contribute to the observed decreased incidence of chronic disease (see Ref. 29 for review) and improvement in aging-associated declines in function (39) in those that are physically active. It is also thought that improvements in metabolic and cardiovascular disease progression after treatment with pharmaceuticals, such as thiazolidinediones (6), or nonpharmaceutical treatments, including caloric restriction (37), are at least partially mediated by increases in mitochondrial biogenesis and function.

The focus of this review is to examine current research regarding common prescription and nonprescription drug interactions on mitochondrial turnover and function, specifically in skeletal muscle. We identified a need for a review of the area because of problems we have encountered when determining inclusion/exclusion criteria for studies of exercise, mitochondria, and aging. Sympathetic nervous system β-adrenergic blockers, nonsteroidal anti-inflammatory drugs (NSAIDs) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) will be considered, as these are the three classes of compounds that we see most commonly when screening older subjects for our studies. The present review includes discussion of measures of mitochondrial size and function and focuses on in vivo studies performed in animal models and humans. The focus on whole organisms is not meant to take away from the importance of cell culture systems for studying drug-induced mitochondrial toxicity, as these studies have provided important insight into pharmacotoxicity and mitochondria (16, 30, 49). Mitochondrial protein turnover is a subtraction of muscle protein turnover, and studies that include alterations to mixed protein turnover will be included due to possible effects on the mitochondrial fraction. As much as possible, the methods used to measure mitochondrial biogenesis [e.g., changes in mitochondrial DNA (mtDNA), respiratory activity, protein content, etc.] are included in this text; however, the reader is encouraged to obtain the original source for further clarification of specific procedures. PubMed Central was used to search the National Center for Biotechnology Information databases using keywords, including “mitochondria”, “mitochondrial biogenesis”, “protein turnover”, “drug”, “interactions”, “exercise”, “adaptations”, and the specific classes and names of drugs. A recently published book entitled, Drug Induced Mitochondrial Dysfunction provides additional information on drug interactions and mitochondrial toxicity, including guidance for laboratory methodology (17).
MITOCHONDRIAL BIOGENESIS

Mitochondrial biogenesis refers to changes in the volume, number of mitochondria per mass unit of muscle, or protein and lipid composition of mitochondrial membranes. Mitochondrial biogenesis is well known to occur following exercise training and results in an increased capacity for ATP production (22). However, viewing mitochondria in reference to cellular energy status overlooks important roles of mitochondria in managing oxidative stress and apoptosis. Indeed, the generation of apoptotic signals and reactive oxygen species is central to theories of aging and may mediate progression of disease and disability (4, 21, 55). Other authors have presented detailed reviews of mitochondrial biogenesis (23, 26, 53), but key components of the process are briefly highlighted here to provide the background for the discussion of drug interactions with exercise adaptations that will follow.

Mitochondrial biogenesis is the result of a highly complex, coordinated effort that results in expression of proteins encoded by both the nuclear (nDNA) and mitochondrial genomes (mtDNA). Although smaller than the nuclear genome, mtDNA (~16.5 kb) encodes for 13 subunits within complexes I, II, IV, and V that are required for electron transport chain (ETC) respiration (53). The coordination of the two genomes to make functional mitochondria appears to involve the transcription factor peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) (35). When PGC-1α is overexpressed in myotubes, there is an increase in mitochondrial biogenesis (70), while PGC-1α knockout mice display decreased mRNA for mitochondrial proteins (36). PGC-1α is also increased following exercise (48), and impairing the response of PGC-1α hinders mitochondrial adaptations (34). It is important to note that, although responses to exercise are decreased compared with wild-type littermates, PGC-1α knockout mice show mitochondrial adaptations, indicating other factors influence mitochondrial biogenesis (34).

Although the signaling pathways regulating mitochondrial biogenesis are not fully elucidated, it is well established that exercise exerts at least some of its beneficial health effects by inducing mitochondrial biogenesis. It is also clear that some of these mitochondrial biogenic pathways are primary or secondary drug targets. The present review will explore where drug and exercise interactions occur to better optimize the combination of drugs and exercise for therapeutic treatment.

β-BLOCKERS

An estimated 50 million people in the United States, and 1 billion people worldwide (11, 27) are hypertensive (blood pressure > 140/90 mmHg). Furthermore, data from the Framingham Heart Study indicate people who are normotensive at 55 yr are at a 90% residual lifetime risk for developing hypertension (62). Lifestyle modification is the primary recommendation to reduce blood pressure; however, modification is routinely used in combination with pharmaceutical treatments, such as diuretics, angiotensin converting enzyme inhibitors, and β-adrenergic receptor antagonists. Of these drug classes, β-adrenergic antagonists have a strong potential to affect mitochondrial biogenesis by impairing aerobic exercise capacity, as well as inhibiting the postexercise PGC-1α response.

β-Adrenergic receptor blockers (β-blockers) effectively treat hypertension by antagonizing the effects of β-adrenergic receptor stimulation by the sympathetic nervous system and circulating catecholamines. β-Blockers function by inducing vasodilation of vascular smooth muscle cells (predominantly via β2-receptors) or reducing cardiac rate and contractility (predominately β1). Nonselective β-blockers antagonize all classes of β-adrenergic receptors (β1–3 and putatively β3) with various affinities (3, 50). Common β-blockers are β1-selective (metoprolol, atenolol), β2-selective (ICI 118551), or nonselective (carvedilol, propranolol), with the latter class often having a greater affinity for β1-receptors (3, 50). Importantly, skeletal muscle predominantly expresses β2-receptors. Therefore, use of a nonselective β-blocker can limit aerobic exercise performance by antagonizing both cardiovascular (β1) and skeletal muscle (β2) responses to exercise.

The effects of β-blockade on adaptations to aerobic exercise have been studied in both healthy and hypertensive subjects. Maximum oxygen consumption (\(V_{O2\text{max}}\)), cardiac output, and stroke volume are common primary outcomes; however, a few studies have evaluated mitochondrial function from skeletal muscle biopsies. We focus on \(V_{O2\text{max}}\) and mitochondrial function results, since \(V_{O2\text{max}}\) is a strong indicator for health and is affected by mitochondrial adaptations. β-Blockers decrease endurance exercise capacity, which may be mediated by interactions with mitochondrial adaptations (Fig. 1).

It is known that β-blockers impair the expected adaptations to aerobic training. For example, Ades et al. (1) evaluated 10

![Fig. 1. Interactions of β-blockers and mitochondrial biogenesis. Aerobic exercise activates β2-adrenergic receptors (β2-AR) on skeletal muscle and induces peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) transcription, a regulator of mitochondrial biogenesis. Selective and nonselective β-blockers can blunt β2-AR signaling, which restricts the expected PGC-1α response following exercise and can impair adaptations to mitochondrial and aerobic capacity. \(V_{O2\text{max}}\), maximum oxygen consumption.](http://jap.physiology.org/)
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wk of endurance training (50 min, 4 times/wk, 75%–85% \(\text{VO}_{2\text{max}}\)) with \(\beta_1\)-selective (metoprolol) and a nonselective \(\beta\)-blocker (propranolol) on cardiac and skeletal muscle adaptations in hypertensive adults (46.5 ± 7 yr). The placebo group showed an increase (+24%, \(P < 0.05\)) in \(\text{VO}_{2\text{max}}\) that was attenuated with \(\beta_1\)-blockade (+8%, \(P < 0.05\)) and completely absent in the nonselective \(\beta\)-blocker group (1). These results provide evidence that aerobic training adaptations may be attenuated with \(\beta\)-blockade and suggest that the nonselective inhibitors, which also antagonize \(\beta_2\)-receptors, can restrict aerobic training effects. However, from these results, it is not possible to distinguish whether the inhibition was a mitochondrial effect.

Mitochondrial adaptations to endurance exercise may be attenuated concomitantly with aerobic adaptations while on \(\beta\)-blockade. Six weeks of aerobic training (50 min 3 times/wk, 85% \(\text{VO}_{2\text{max}}\)) increased \(\text{VO}_{2\text{max}}\) in healthy young men (21–35 yr) on a placebo (+16%, \(P < 0.05\)) to a greater extent than a \(\beta_1\)-selective (+6%, \(P < 0.05\)) or nonselective \(\beta\)-blocker (no change) (69). Mitochondrial function (succinate dehydrogenase and citrate synthase activity) also showed the greatest increase while on placebo, with attenuated responses in both \(\beta\)-blocker groups. Similar results were shown by Svedenhag et al. (57) following 8 wk of cycling training (40 min 4 times/wk, 60–75% \(\text{VO}_{2\text{max}}\)) in young men (20–31 yr). \(\text{VO}_{2\text{max}}\) increased for placebo and nonselective \(\beta\)-blocker groups, but cytochrome-c oxidase and 3-hydroxyacyl-CoA dehydrogenase increased to a greater extent in placebo (+87 and +63%, respectively) than \(\beta\)-blocker (+38 and +22%, respectively).

The results discussed above reveal differences in aerobic training adaptations between \(\beta_1\)-selective and nonselective \(\beta\)-blockers in humans. Data from rodent studies confirm that \(\beta_2\)-blockade may impair the adaptation to endurance exercise to a greater extent than \(\beta_1\)-blockade. Ji et al. (25) reported 10 wk of treadmill training (26.8 m/min, 15% grade for 60 min, 5 times/wk) in rats increased skeletal muscle activity of enzymes in the tricarboxylic acid cycle (citrate synthase and malate dehydrogenase), ETC (cytochrome-c oxidase), and fatty acid oxidation (hydroxyacyl coenzyme A dehydrogenase) activity in placebo and \(\beta_1\)-selective treatment, but there was no change in any of these with nonselective \(\beta\)-blockade. However, a rate-limiting enzyme of fatty acid oxidation (carnitine palmitoyl transferase) was increased in all three groups, indicating that mitochondrial enzyme adaptations can occur during \(\beta\)-blockade, possibly dependent on substrate availability (25). Collectively, these results suggest \(\beta\)-blockade can impair training-induced activities of mitochondrial enzymes in skeletal muscle and the additional nonselective blockade of \(\beta_2\)-receptors, having a more restrictive effect.

Recent evidence provides insight into a potential mechanism of \(\beta_2\)-receptor activation and mitochondrial adaptations through PGC-1α. Data collected from mice demonstrate that \(\beta_2\)-selective activation (clenbuterol) increases PGC-1α mRNA under resting conditions, but this effect was not evident during selective stimulation of α-, \(\beta_1\)-, or \(\beta_2\)-receptors, or in transgenic mice lacking \(\beta\)-adrenergic (42). Furthermore, \(\beta_2\)-blockade inhibited PGC-1α mRNA transcription following a 45-min bout of treadmill running, an effect that was reversed with \(\beta_2\)-stimulation (42). Interestingly, the same authors followed their initial results with a novel finding of multiple isoforms of PGC-1α and demonstrated that both \(\beta_2\)-agonists and endurance exercise induced PGC-1α-b and PGC-1α-c, but not PGC-1α-a (41). Thus it appears that PGC-1α can be regulated by \(\beta_2\)-adrenergic stimulation or blockade.

In summary, \(\beta\)-adrenergic blockade can impair \(\text{VO}_{2\text{max}}\) and mitochondrial adaptations to endurance exercise (Fig. 1). However, the effects are variable and may, at least in part, depend on the receptor specificity of the \(\beta\)-blocker. The impaired mitochondrial response to exercise training with nonselective \(\beta\)-blockers may be due to a \(\beta_2\)-receptor-mediated decrease in PGC-1α. Therefore, the potential for impaired exercise capacity associated with \(\beta\)-blockade and the potential for attenuated mitochondrial adaptations mediated by \(\beta_2\)-blockade should be considered when prescribing \(\beta\)-adrenergic antagonist therapy.

HMG-CoA REDUCTASE INHIBITORS

HMG-CoA reductase inhibitors (statins) are commonly prescribed for patients with hypercholesterolemia (total cholesterol >200 mg/dl), with 24 million prescriptions filled in the United States during 2003–2004 (38). The primary mechanism of statins is to inhibit the rate-limiting step for cholesterol synthesis, the conversion of HMG-CoA to mevalonate by the enzyme HMG-CoA reductase. The inhibition of HMG-CoA reductase by statins can effectively reduce circulating cholesterol concentrations and may also have beneficial effects on other cardiovascular disease risks, further reinforcing the use of statins in the treatment of cardiovascular disease (13).

Although statin treatments are highly effective and generally free of clinically relevant incidents, the most common side effect of statin treatments is skeletal muscle myopathies ranging from mild pain, weakness, and decreased function, to very rare but fatal cases of rhabdomyolysis (0.15 deaths in 1 million) (58).

While statin treatments are considered free of serious side effects (death, severe functionally impairment), epidemiological data have shown ~10% of patients on statins (40–80 mg/day) report at least mild muscular symptoms after 1 mo of beginning therapy (8). Additionally, ~38% of those with symptoms reported pain with moderate exertion during activities of daily living (8). Biopsy samples from four patients with statin-associated myopathy revealed histological evidence for mitochondrial dysfunction, including ragged red fibers, negative staining for cytochrome-c oxidase, and increased lipid accumulation. These effects were reversed following administration of a placebo (47). Interestingly, all four patients were able to correctly identify placebo vs. return to statin treatment. It is possible that statin-induced myopathies are mediated through mitochondria (Fig. 2). Initial research evaluated the possibility of ubiquinone depletion as mediating statin-induced skeletal muscle myopathies.

The product of HMG-CoA reductase, mevalonate, is not only used as a precursor for cholesterol, but also for multiple downstream products, such as ubiquinone, dolichol, and intermediates of the cholesterol synthesis pathway that are used for isoprenylation of proteins (2, 44). The decreased activity of HMG-CoA reductase by statin treatment decreases flux through the cholesterol synthetic pathway and potentially has further reaching effects than simply lowering circulating cholesterol concentrations. For example, ubiquinol, the reduced form of ubiquinone, functions as an electron shuttle between the flavoproteins and cytochromes in the ETC. A branch point
of cholesterol synthesis is the formation of farnesyl pyrophosphate that can be used to synthesize ubiquinone for the ETC or squalene for eventual cholesterol formation. Inhibition of HMG-CoA reductase can decrease the formation of isopentenyl diphosphate units needed for ubiquinone formation. In addition to sharing a common pathway, ubiquinone is transported by low-density lipoprotein cholesterol. A combination of impaired synthesis and a decrease in low-density lipoprotein cholesterol most likely contribute to the decreased concentration of circulating ubiquinone observed following statin treatment (13, 18, 31, 52).

Intramuscular ubiquinone concentrations are less well characterized and may not respond to statin treatment in a similar fashion to circulating levels. Indeed, statin treatment in humans has shown inconsistent effects, with reports of decreases (45), increases (32), and no change (31) on skeletal muscle concentrations of ubiquinone. The difference in effects on ubiquinone concentration may be related to differences in treatment doses and pharmacokinetics of the drugs. For example, Lamperti et al. (33) evaluated skeletal muscle concentrations of ubiquinone and cytochrome-c oxidase in hypercholesterolemic patients receiving low doses of statins (5–20 mg/day of a variety of statins) and did not show differences compared with control subjects in either variable. In contrast, higher doses of simvastatin (80 mg/day) for 8 wk decreased intramuscular ubiquinone and decreased respiratory activity (~24 to ~74%) of complexes II-IV and citrate synthase, with no changes shown in groups receiving atorvastatin (40 mg/day) or placebo (45). It is important to note that these later findings by Paiva et al. (45) were not significant after normalizing ETC activity for changes in citrate synthase activity, suggesting that the changes in complex activity are explained by decreased mitochondrial content. In a follow-up report, the simvastatin treatment resulted in a decrease in the ratio of mtDNA to nDNA, providing further support that changes in mitochondrial respiratory capacity were due to decreased mitochondrial content (54). Recent data from embryonic zebra fish showed lovastatin treatment decreased mitochondrial function (determined via MitoTracker and fluorescence-activated cell sorting) in a dose-dependent manner (19). The effect was abolished with concomitant trans-

The variability in peripheral exposure to bioactive statin metabolites may contribute to varied responses of skeletal muscle concentrations of ubiquinone and mitochondria respiratory activity. For example, Lamperti et al. (33) evaluated skeletal muscle concentrations of ubiquinone and cytochrome-c oxidase in hypercholesterolemic patients receiving low doses of statins (5–20 mg/day of a variety of statins) and did not show differences compared with control subjects in either variable. In contrast, higher doses of simvastatin (80 mg/day) for 8 wk decreased intramuscular ubiquinone and decreased respiratory activity (~24 to ~74%) of complexes II-IV and citrate synthase, with no changes shown in groups receiving atorvastatin (40 mg/day) or placebo (45). It is important to note that these later findings by Paiva et al. (45) were not significant after normalizing ETC activity for changes in citrate synthase activity, suggesting that the changes in complex activity are explained by decreased mitochondrial content. In a follow-up report, the simvastatin treatment resulted in a decrease in the ratio of mtDNA to nDNA, providing further support that changes in mitochondrial respiratory capacity were due to decreased mitochondrial content (54). Recent data from embryonic zebra fish showed lovastatin treatment decreased mitochondrial function (determined via MitoTracker and fluorescence-activated cell sorting) in a dose-dependent manner (19). The effect was abolished with concomitant trans-

Fig. 2. Statin-induced skeletal myopathies may originate with mitochondrial dysfunction. The decreased flux through the cholesterol biosynthesis pathway with statin therapy can impair production of necessary components of the electron transport chain, including isoprenylated proteins (for membrane attachment), heme A (necessary for complex-IV), and ubiquinone (electron shuttle). Statins may also negatively affect mitochondria by increasing apoptosis [via B-cell CLL/lymphoma 2 (Bcl-2)] and protein degradation (via atrogin-1). A combination of diminished functional respiratory chain components and proapoptotic environment can lead to statin-induced mitochondrial dysfunction. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.
fection with PGC-1α cDNA, suggesting that stimulation of mitochondrial biogenesis may protect against statin-induced impairments in mitochondria function (19). Thus, although high-dose statin therapy could impair mitochondrial function through depletion of muscle ubiquinone, the primary mechanism for statins to impair mitochondria function may be mediated through apoptosis and decreased mitochondrial content.

In addition to respiratory chain activity effects, evidence exists suggesting that apoptosis pathways may contribute to statin-associated myopathies. Mitochondrial-initiated apoptosis is thought to be influenced by the net contribution of pro- vs. antiapoptotic members in the B-cell CLL/lymphoma 2 (Bcl-2) family of proteins. The anti-apoptotic Bcl-2 subfamily includes Bcl-2, Bcl2-like 1 (Bcl-XL), and myeloid cell leukaemia sequence-1 (Mcl-1), while proapoptotic subfamilies include the Bcl-2 associated-X (Bax) proteins. Bax proteins are induced by BH3 interacting domain death agonist proteins to form channels in the outer membrane that release apoptosis-promoting factors (including cytochrome-c and apoptosis-inducing factor). Bcl-2 and Bcl-XL proteins inhibit channel formation. The detrimental effects of statins are suggested to be induction of a proapoptotic state by downregulation of the antiapoptotic Bcl-2 protein (5) and Mcl-1, a Bcl-2 homolog (5, 15). In cell cultures, the decrease in Bcl-2 with statins can be reversed upon treatment with farnesyl pyrophosphate and geranyl-geranyl pyrophosphate, suggesting that isoprenoid intermediates have a role in statin-induced apoptosis (5).

Statins may also promote muscle fiber atrophy, specifically through atrogin-1, a muscle-specific ubiquitin ligase. Recent evidence from human muscle samples showed atrogin-1 mRNA is increased with statin therapy (19). Atrogin-1 null myotubes and zebra fish embryos appear to be resistant to statin-induced damage, suggesting atrogin-1 plays an important role in statin myopathies (19). Thus mitochondrial-induced apoptosis or skeletal muscle atrophy may contribute to statin-induced skeletal muscle myopathies.

The alterations to mitochondrial content and function discussed above likely play a role in contributing to skeletal myopathies that can occur during statin therapy. The known side effects of muscle pain and weakness can impair mobility or exercise capacity and may hinder functional capacity of patients. Indeed, leg strength was reduced in four older patients while on statin therapy, but improved within 2 wk of stopping treatment (47). On return to treatment, each patient reported muscle pain and weakness again. The effect of four different statin treatments on muscle pain and weakness has also been evaluated in professional athletes with familial hypercholesterolaemia (56). Out of 22 athletes, 16 were not able to tolerate statin treatment of any form due to adverse muscle symptoms. These were relieved in 1–3 wk following removal of treatment and indicate statins can induce muscle myopathy in athletes.

In summary, statins have the potential to adversely affect aerobic exercise tolerance, possibly through impaired mitochondrial function, decreased mitochondrial content, and apoptotic pathways. Although clinically serious myopathies are rare side effects of statin therapy, minor impairments to mitochondrial function that do not elicit severe symptoms could hinder mitochondrial adaptations to aerobic exercise. Thus mitochondrial adaptations, which are a primary response to aerobic exercise, could be limited in patients who are consuming statins.

NSAIDs

NSAIDs are a generic class of common nonprescription medications with analgesic, antipyretic, and antiinflammatory capabilities. Ibuprofen, acetaminophen, and aspirin are regularly consumed NSAIDS and have an estimated 25 million users everyday (66). The primary mechanism of NSAIDs is to impair the activity of cyclooxygenase (COX), which produces proinflammatory prostaglandins (PGs) from arachidonic acid. NSAIDs competitively bind to the arachidonate binding site of COX to decrease formation of PGs. The COX family has constitutive (COX-1) and inducible (COX-2) isoforms, with additional variants of each. A putative COX-3 isoform has been identified as an intron-retaining version of COX-1 and is also sensitive to COX inhibitors, thus providing a mechanism of action for drugs that do not target COX-1 or COX-2 (9). NSAIDs can induce negative gastrointestinal side effects due to inhibition of COX-1 located within the endothelium of the stomach and kidneys (64). In an effort to avoid gastrointestinal side effects, selective COX-2 inhibitors (e.g., Celebrex and Vioxx) were developed to decrease COX-2 activity, which is locally induced at sites of inflammation (64).

NSAIDs have the potential to impair mitochondrial function through a variety of mechanisms (Fig. 3). In vitro models have shown that NSAIDs can inhibit β-oxidation and promote uncoupling of oxidative phosphorylation (43), while in vivo human studies have shown decreased postexercise skeletal muscle protein synthesis compared with placebo (60). The effects of NSAIDs on in vitro oxidative phosphorylation and in vivo protein synthesis will be considered separately.

NSAIDs and In Vitro Mitochondrial Function

The carboxyl group and lipid soluble nature of NSAIDS allow the drug to pass through the mitochondrial membranes and act as a protonophore to disrupt the membrane potential across the inner membrane. NSAID exposure to isolated mitochondria from rat liver showed increased proton leak and decreased rates of ATP synthesis (30). In agreement, mitochondria isolated from rat kidneys also showed uncoupled oxidative phosphorylation following NSAID treatment (40).

The extent of uncoupling may be due to the pKa of the acid group. Nulton-Persson et al. (43) showed that salicylic acid (the primary metabolite of acetylsalicylic acid or aspirin) exerted a larger inhibition of state 3 respiration than acetylsalicylic acid in mitochondria isolated from rat hearts. It is important to note that the doses of salicylic acid and acetylsalicylic acid used by Nulton-Persson et al. were in the range of estimated plasma concentrations during therapeutic use (low millimolar concentrations), suggesting that mitochondrial inhibition may occur with commonly consumed doses. The study further reported that salicylic acid and acetylsalicylic acid were both able to inhibit a rate controlling Kreb’s cycle enzyme, α-ketoglutarate dehydrogenase. However, the inhibitory effects of salicylic acid, but not acetylsalicylic acid, could be reversed with increased concentrations of the substrate α-ketoglutarate (43). Collectively, these in vitro results indicate that aspirin can impair mitochondrial function, but the inhibitory characteristics can vary between metabolites of the drug.

In addition to uncoupling oxidative phosphorylation, NSAIDs can also impair mitochondrial function by inducing oxidative stress. Mice injected with a high dose (300 mg/kg
Exercise

PGF$_{2\alpha}$

Cyclooxygenase

Mixed Muscle Protein Synthesis

Subfractional FSR
- myofibrilar
- sarcoplasmic
- mitochondrial

NSAIDs

↑Bax
↓Bcl-2

Pro-apoptosis

Cell Cycle Arrest

↓ Cell proliferation

Fig. 3. Nonsteroidal anti-inflammatory drugs (NSAIDs) can impair mixed muscle protein synthesis and may decrease the fractional synthetic rate (FSR) of mitochondrial proteins. Exercise promotes muscle protein synthesis, including the mitochondrial fractional synthesis rate. Prostaglandin (PG) F$_{2\alpha}$ production by cyclooxygenase appears to be a necessary stimulus for protein synthesis; however, NSAIDs inhibit cyclooxygenase activity and block PGF$_{2\alpha}$ production. NSAIDs can also induce cell cycle arrest and apoptosis, leading to decreased cell proliferation and subsequently decreased mixed muscle FSR, which includes the mitochondrial fraction. NSAIDs can impair mitochondrial adaptations to exercise by attenuating protein synthesis and promoting protein breakdown. Bax, Bcl-2 associated X.

body wt) of acetaminophen showed increased liver mtDNA damage, with concomitant increases in the highly reactive species peroxynitrite compared with control mice (12). The mitochondria also showed much greater protein nitration than other cellular locations (nucleus, cytosol, microsomes), suggesting that mitochondria are a site for oxidative damage, presumably due to accelerated peroxynitrite production (12). Injection with glutathione either immediately or 1.5 h after acetaminophen injection blunted the effects of the drug treatment, suggesting that oxidative stress may be mediating the adverse drug effects (12). Although the dose of acetaminophen represents a hepatotoxic dose and was much higher than commonly consumed, the results indicate mitochondrial-induced oxidative stress and mtDNA damage can occur with NSAID treatment.

Mitochondrial-mediated apoptosis may also be stimulated by NSAIDs. Aspirin is being investigated for its ability to stimulate apoptosis through both extrinsic and intrinsic pathways. The intrinsic mechanism is suggested to be through generation of a proapoptotic environment by upregulating Bax and downregulating Bcl-2 proteins (16). Neuronal cell cultures had concentration-dependent decreases in cell survival with aspirin treatment (2.5–50 mM aspirin) and parallel increases in cytochrome-c release and caspase-3 and -9 activities (16). Similar increases were also observed in the proapoptotic Bax and proteins involved in cell cycle arrest (p53 and p27$^kip1$), suggesting that aspirin promotes cell cycle arrest and apoptosis in concentrations of 2.5–50 mM. Although the upper range (>10 mM) of these aspirin concentrations are higher than circulating concentrations (~1–10 mM), the lower concentrations of aspirin (2.5–10 mM) still exerted negative effects, suggesting physiological concentrations of aspirin may promote apoptosis and cell cycle arrest (16, 43).

NSAIDs and In Vivo Protein Synthesis

It is clear that NSAIDs can impair cell survival and mitochondrial function in cell cultures and animal models. The negative effects of NSAIDs on mitochondrial function may also occur through impairments to skeletal muscle protein synthesis. Mitochondrial protein synthesis is a fractional component to mixed muscle protein synthesis; therefore, any decreases in mixed muscle protein synthesis could also include decreased mitochondrial protein synthesis. Recent evidence in humans identify that NSAIDs can impair mixed muscle protein synthesis following resistance exercise through a COX-mediated mechanism (65). Although mitochondrial adaptations are commonly considered adaptations to aerobic exercise, resistance exercise has been shown to increase mitochondrial protein synthesis (67) and should be included when evaluating the potential of drugs to impair exercise-induced mitochondrial biogenesis.

COX-1 and COX-2, but not COX-3, mRNA are increased following resistance exercise in humans (65). All isoforms of COX act on arachidonic acid liberated from lipid membranes to produce PGH$_2$, which is further modified to active forms, including PGF$_{2\alpha}$ (7). PGF$_{2\alpha}$ mediates skeletal muscle growth by participating in myoblast fusion and multinucleation of fibers (24). In human skeletal muscle, PGF$_{2\alpha}$ is increased (~60%) following eccentric resistance exercise, an effect that is abolished with acetaminophen or ibuprofen (59). Additionally, these drugs also attenuate the postexercise increase in fractional synthetic rate of mixed skeletal muscle protein 24 h following high-intensity resistance exercise (60). Thus COX inhibition can impair mixed skeletal muscle protein synthetic response to resistance exercise. Since mitochondrial protein synthesis is a subfraction of mixed muscle protein synthesis, and these studies did not separate the mitochondrial fraction, the effects of NSAIDs on mitochondrial protein synthesis are not known. Early results from an isolated mitochondrial fraction from rat liver showed decreased basal rates of incorporation of a radioactive leucine tracer with increasing concentrations of salicylate (0.6–20 mM) and suggest that aspirin may impair mitochondrial protein synthesis (14). The inhibitory effects on leucine incorporation were concentration dependent,
beginning at low concentrations (−66% inhibition at 0.6 mM), which is within the estimated circulating concentration following aspirin consumption (14, 43). Thus NSAIDs can impair mixed protein synthesis following resistance exercise, which may include negative effects on the mitochondrial fractional synthesis rate.

In summary, data from in vitro and animal models demonstrate that NSAIDs can impair mitochondrial function by uncoupling oxidative phosphorylation and can induce mitochondrial-mediated apoptosis. Furthermore, NSAIDs can impair protein synthesis following resistance exercise and may subsequently impair mitochondrial function.

CONCLUSIONS, FUTURE DIRECTIONS, AND RECOMMENDATIONS

As research continues to evaluate mitochondrial function and potential countermeasures for dysfunction, the effects of drugs on mitochondria content and activity will need to be considered. This review has presented a brief background and evidence for drugs that are commonly consumed and subsequently encountered by researchers and clinicians. Increasing physical activity is a common lifestyle recommendation for hypertension and hypercholesterolemia; however, drugs such as β-blockers and statins that are commonly prescribed for their treatment have the potential to limit the beneficial effects of exercise on mitochondria. Similarly, NSAIDs used to ameliorate postexercise pain or decrease cardiovascular disease risk may also impact skeletal muscle recovery from exercise.

In this brief review, only a small subset of common medications were discussed. Many of the findings discussed herein were limited in their interpretation to skeletal muscle effects rather than mitochondria per se. Although evidence was presented that these medications may affect mitochondria function, there is need for mitochondrial-specific study designs. In addition, experiments should be designed to evaluate the impact of pharmaceutical compounds during rest, exercise, and postexercise recovery, with emphasis on the postexercise period, since this is when most exercise-induced adaptations occur.

Population-specific designs (e.g., young, aged, obese) should also be considered when examining potential exercise and drug interactions. It is realistic to expect that treatment in one population, where mitochondrial or exercise function is optimal, may differ from other populations, where mitochondrial or exercise function is compromised. Careful attention must also be paid to the drugs used by study participants, with clear indication of the medications in the resulting publication. For those who prescribe exercise to patients, careful attention must be paid to the drugs patients are using and what the intended goal of drug/exercise treatment is. Finally, researchers, especially those investigating exercise and chronic disease, should continue to explore the interaction between drugs, exercise, and mitochondrial adaptation. It can if it be determined where detrimental effects occur, it may be possible to eliminate negative interactions to facilitate the transition to a state of health based on exercise rather than medication.

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REFERENCES


