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Review

Drug induced mitochondrial dysfunction: Mechanisms and adverse clinical consequences

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ABSTRACT

Several commonly used medications impair mitochondrial function resulting in adverse effects or toxicities. Drug induced mitochondrial dysfunction may be a consequence of increased production of reactive oxygen species, altered mitochondrial permeability transition, impaired mitochondrial respiration, mitochondrial DNA damage or inhibition of beta-oxidation of fatty acids. The clinical manifestation depends on the specific drug and its effect on mitochondria. Given the ubiquitous presence of mitochondria and its central role in cellular metabolism, drug-mitochondrial interactions may manifest clinically as hepatotoxicity, enteropathy, myelosuppression, lipodystrophy syndrome or neuropsychiatric adverse effects, to name a few. The current review focuses on specific drug groups which adversely affect mitochondria, the mechanisms involved and the clinical consequences based on the data available from experimental and clinical studies. Knowledge of these adverse drug-mitochondrial interactions may help the clinicians foresee potential issues in individual patients, prevent adverse drug reactions or alter drug regimens to enhance patient safety.

Contents

Abbreviations: ETC, electron transport chain; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; Cyt C, cytochrome C; $O2^{-}$, superoxide radical; H2O2, hydrogen peroxide; MnSOD, manganese superoxide dismutase; GSPx, glutathione peroxidase; $ONOO^{-}$, Peroxynitrite; OH•, hydroxyl radical; NO, nitric oxide; mtNOS, mitochondrial nitric oxide synthase; IMM, inner mitochondrial membrane; mPTP, mitochondrial permeability transition pore; VDAC, voltage dependent anion channel; ANT, adenine nucleotide translocase; Cyp-D, cyclophilin D; AIF, apoptosis inducing factor; EndoG, endonuclease G; nDNA, nuclear DNA; OXPHOS, oxidative phosphorylation; POLG, polymerase gamma; CPT, carnitine palmitoyl transferase; FAD, flavin adenine dinucleotide.

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1. Introduction

Advances in therapeutics have been paralleled by an increasing realization of the potential adverse consequences of drug therapy. Data estimates from the United States of America and Europe show that more than 100,000 people die annually due to drug related causes (Centers for Education and Research on Therapeutics, 2016; European Commission, 2008). While a majority of the population would benefit from rational drug therapy, it is imperative to recognize the possible adverse effects of drugs, the mechanisms involved and adopt an approach to minimize any harmful consequences. Major changes have taken place over the last couple of decades in terms of screening for adverse effects of drugs during the various stages of drug development. Nonetheless, the safety data obtained during clinical drug development are limited because the number of patients exposed to the drug is small compared to the intended population in which it would be used. Drug-induced adverse effects are a frequent cause for the withdrawal of many drugs from the market post United States Food and Drug Administration approval (Siramshetty et al., 2016). Regardless of the fact that multiple mechanisms are involved in drug induced adverse reactions (Uetrecht and Naisbitt, 2013), accumulating data suggest that mitochondria, either as a primary or a secondary target to drug, and their dysfunction, plays an important role in drug induced adverse effects (Szewczyk and Wojtczak, 2002).

Impaired mitochondrial function is associated with aging (Bratic and Larsson, 2013) as well as many pathological states including cancer (Boland et al., 2013), sepsis (Singer, 2014), obesity (Bournat and Brown, 2010), and diabetes (Sivitz and Yorek, 2010). Conversely, some of the drugs used in the treatment of these conditions can themselves impair mitochondrial function. While some drugs affect mitochondria directly (inhibit electron transport chain [ETC], mitochondrial DNA [mtDNA] transcription, protein production and ATP synthesis) others cause indirect toxicity to mitochondria (by increasing reactive oxygen species [ROS] production which in turn cause mtDNA mutations, membrane depolarization and decreased antioxidant production). For example, troglitazone, a drug used to treat type 2 diabetes mellitus was withdrawn from the market due to hepatotoxicity. Later studies revealed that a potential mechanism behind the liver damage was mtDNA damage, mitochondrial permeability induction and impaired ATP production (Rachek et al., 2009; Okuda et al., 2010). Cerivastatin, a lipid-lowering drug, was withdrawn from the market due to drug related fatal rhabdomyolysis leading to renal failure. Impaired skeletal muscle mitochondrial respiration, beta-oxidation, increased mitochondrial swelling, cytochrome C (Cyt C) release and DNA fragmentation have been shown to be associated with rhabdomyolysis (Kaufmann et al., 2006; Golomb and Evans, 2008). Hence, there are sufficient grounds to investigate the role of drugs in inducing mitochondrial dysfunction and the resulting potential adverse effects or toxicities. Experimental evidence of drug induced mitochondrial dysfunction need not necessarily have direct clinical implications. However, there are well established evidences of mitochondrial toxicities due to commonly used medications, which manifest clinically. Knowledge of these adverse drug-mitochondrial interactions may help the clinicians design safer therapeutic regimens in individual patients.

The role of mitochondrial toxicity in drug induced organopathies (Begriche et al., 2011; Varga et al., 2015) has been already reviewed. Mitochondria as a drug target for therapeutic benefit has also been reviewed (Szewczyk and Wojtczak, 2002). The present review focuses on the various drugs, which have an adverse impact on mitochondrial function, the mechanisms and their clinical manifestations. Data based on currently available translational and clinical research are provided for each drug group. The drugs have been listed according to the pharmacological groups they belong to. Hence, two drugs which produce similar mitochondrial toxicity may be listed in different groups and the clinical outcome might be different.

2. Mechanisms of mitochondrial dysfunction

The key sites of drug action in the mitochondria, the mechanisms of drug induced mitochondrial dysfunction and the consequences are illustrated in Figs. 1 and 2. The major mechanisms are described here.

2.1. Over production of reactive oxygen species (ROS)

ROS released by drugs, directly or indirectly, play a major role in drug induced toxicity (Kovacic and Cooksy, 2005; Deavall et al., 2012). ROS can be released by both exogenous and endogenous sources. Exogenous sources include drugs, nanomaterials, xenobiotics or ionizing radiation (Riley, 1994; Pagano, 2002; Deavall et al., 2012; Fu et al., 2014). Most of the endogenous ROS are mainly produced from complex I and III of mitochondria during ATP synthesis in the form of superoxide radical ($\cdot O2^-$) and hydrogen peroxide (H_2O_2) (Liu et al., 2002; Murphy, 2009). Under normal conditions the $\cdot O2^-$ produced is detoxified by mitochondrial manganese superoxide dismutase (MnSOD) to produce H_2O_2. Using reduced glutathione, the enzyme glutathione peroxidase (GSPx) converts H_2O_2 to water, thus completely scavenging the ROS produced within the mitochondria. However, when there is an imbalance between the cell antioxidant defense mechanisms and production of ROS due to exposure to toxic agents (drugs) or disease there is cell damage. Much of the damage is due to peroxynitrite ($ONOO^-$) and hydroxyl radical (OH•) (Liochev and Fridovich, 1994; Liochev and Fridovich, 1999; Radi et al., 2002). Both $\cdot O2^-$ and H_2O_2, itself are not reactive but when they react with nitric oxide (NO) and metal ions such as Fe^{2+} and Cu^+ respectively, they form a highly reactive $ONOO^-$ and OH•. Both these free radicals have detrimental cellular effects on mtDNA, oxidation of proteins, lipids, mitochondrial ETC complexes, and mitochondrial membrane integrity (Radi et al., 2002; Turrens, 2003). Damage to mtDNA lead to transcriptional errors resulting in the synthesis of defective mitochondrial proteins (Cline, 2012) which subsequently increase ROS production. Accumulation of ROS in turn causes oxidative stress (Yakes and Van Houten, 1997) and activation of mitochondrial mediated apoptotic pathways (Turrens, 2003; Sinha et al., 2013) causing cell death. Mitochondria also possess an enzyme, mitochondrial nitric oxide synthase (mtNOS), which produce another important free radical species i.e. NO. Increase in NO production itself has several damaging effects on mitochondrial function, particularly on the mitochondrial respiratory chain by causing reversible inhibition of complex IV of the ETC i.e. cytochrome *c* oxidase (Brown and Borutaite, 2002; Ghafourifar and Cadenas, 2005).