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Review Article

Drugs acting on mitochondrial pathways

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ABSTRACT

Mitochondrion, "the power house" of the cell plays a vital role in generating energy for the intricate functions of the cells. Mitochondria also play important roles in various apoptotic pathways. Around 80-90% of the ATP generated in cells is contributed by these organelles through the process of oxidative phosphorylation. Though this process is essential for the functioning of cells it also generates various Reactive Oxygen Species (ROS), which are toxic to cells. Hence mitochondrial dysfunction is hypothesized to be an important factor in the occurrence of disorders related to aging such as neurodegeneration and malignancies. Several commonly used drugs in clinical practice exert their action by interacting with mitochondrial pathways. This review attempts to focus on the various groups of drugs which act on mitochondria and are utilized for therapy of conditions like cancer, diabetes mellitus, neurodegeneration and so on.

Keywords: Apoptosis, Energy production, Mitochondria, Malignancies, Neurodegeneration, Reactive oxygen species

INTRODUCTION

Mitochondria the power house of various processes generating energy in the cell, are also associated with apoptosis and cardioprotection.[1] Around 80- 90% of ATP in the cell is produced by mitochondria through oxidative phosphorylation.[1]

Since oxidative phosphorylation generates reactive oxygen species which are toxic to various cells, it has been hypothesized that mitochondrial dysfunction is a key factor in occurrence of several age related disorders and malignancies.[2]

DRUGS ACTING ON MITOCHONDRIA

Drugs acting on mitochondria have been utilized in several fields of medicine (Table 1). This review will focus on some drugs which protect mitochondrial function and those drugs which cause mitochondrial toxicity. Newer molecules in the pipeline which interact with mitochondria have also been included.

Targeting mitochondria in malignancies

Cancer cells are actively involved in glycolysis and mitochondrial metabolism which are essential for producing substrates (amino acids, lipids glucose) as well as ATP for cellular proliferation.[3] Mitochondrial

metabolism is also stimulated by oncogenic activation to produce ATP and intermediates of TCA cycle which are required for macromolecule synthesis.[4] Some chemotherapeutic agents which act on mitochondria have been described below.

Paclitaxel

In a study done on neuroblastoma cell lines, paclitaxel has been found to act through mitochondria and was shown to produce an increase in reactive oxygen species and stimulate the permeability transition pore (PTP) dependent release of cytochrome c which is an apoptogenic factor, in a caspase independent manner.[5]

By opening the mitochondrial PTP, there is a reduction in mitochondrial membrane potential and Ca^{2+} release from mitochondria, leading to calcium loss, which indicates that some of the acute adverse effects of anti cancer drugs could be due to their effect on mitochondrial function.[6]

Etoposide

The cytotoxic property of etoposide (VP-16) induced cell death has been put forward to induction of apoptosis.[7,8] Several mechanisms have been suggested to identify the signaling pathway for apoptosis.

One such theory is induction of mitochondrial permeability transition (MPT) leading to Ca^{2+} dependent swelling of the mitochondria and depolarization of mitochondrial membrane potential which is prevented by cyclosporine A, a potent inhibitor of MPT.[9] Other proposed apoptotic mechanisms are activation of caspases, release of cytochrome c and decrease in mitochondrial membrane potential.[10,11]

Vinorelbine

Vinorelbine, a semi-synthetic vinca alkaloid, recruits the pro-apoptotic protein BIM to the mitochondria, where it suppresses the anti apoptotic protein BCL2, thereby making cells treated with this drug undergo apoptosis during interphase.[12]

Targeting mitochondria in Neurodegenerative disorders

Various proteins associated with mitochondria such as PTEN-induced putative kinase 1 (PINK1), DJ-1, α-synuclein, leucine-rich repeat kinase 2 and Parkin are implicated in familial Parkinson's Disease.[13]

The association of mitochondria with idiopathic Parkinson's disease was first discovered when a postmortem brain of a PD patient showed a complex-I deficiency in the substantia nigra.[14]

These facts have led to the development of newer treatment options for PD directed at mitochondrial metabolism, one of which is MAO inhibitors.[15] MAO is a fundamental enzyme located in mitochondrial outer membrane, which has two isoforms MAO-A (predominant isoform in non neuronal tissue)and MAO-B (major brain isoform).[15] Both selegiline and rasagiline have been shown to be neuroprotective in many studies.[16] But the efficacy of selegiline in treatment of PD has been offset by the neurotoxic metabolites of this drug and to overcome this disadvantage, another drug with a similar mechanism, rasagiline was discovered.[16] The neuroprotective and anti apoptotic actions of rasagiline is brought about by stimulation of anti apoptotic proteins. As a consequence, the drug binds to the binding site in Flavine Adenine Dinucleotide (FAD) in GAPDH and other similar anti apoptotic proteins.[16]

Dysfunction in mitochondrial metabolism has also been linked to Alzheimer's disease. A reduction in cytochrome oxidase (complex IV) activity in the mitochondria could result in decreased energy stores, leading to the neurodegenerative process.[17] There are various mitochondrial genes which predispose to dementia. In a study done to assess the role of some commonly found mitochondrial DNA haplogroups on dementia risk, it was seen that people who had haplogroup T had a statistically significant risk of developing dementia and haplogroup J exhibited a statistically significant 8 year reduction in Modified Mini-Mental State Examination (3MS) when both were assessed with regard to the common haplogroup H.[18]

Leber's hereditary optic neuropathy (LHON) is an inherited disorder due to mitochondrial DNA mutations presenting with progressive visual loss due to optic atrophy.[19-21] Idebenone, an analogue of co enzyme Q10,has been investigated for its role in the therapy of LHON and Friedrich's ataxia.[20] The first randomized controlled trial performed on idebenone in LHON showed that the drug is safe, well tolerated and benefited people with discordant visual acuities in both eyes, though statistical significance was not attained in the primary end point.[22] This drug has been given authorization for marketing by the European Commission for treatment of LHON in 2015.[23,24]

ROLE OF MITOCHONDRIA IN CARDIO PROTECTION

Ranolazine an anti anginal drug exhibits a protective action on mitochondrial complex I during ischemic reperfusion injury to the heart and decreases damage to complex I indirectly through cytosolic mechanisms which result in improved structural integrity of complex I and reduced its oxidative stress.[25] Similarly the anti hypertensive drug minoxidil exerts its cardioprotective action by activating the ATP sensitive potassium channels situated in the inner membrane of mitochondria (mitoKATP channel) and also reduced the increased mitochondrial Ca^{2+} concentration induced in myocytes by treatment with ouabain.[26]

Role in treatment of parasitic infestations

Atovaquone, an antimalarial drug, also possesses action upon other eukaryotic parasitic organisms such as *Pneumocystis carinii* by blocking the electron transport chain.[27] In addition to the above mechanism, atovaquone produced a collapse of the mitochondrial membrane potential, thereby interfering with respiration of malarial parasite within minutes.[28] Ascofuranone, which is an antibiotic derived from a fungus *Ascochyta visiae*, inhibited *Trypanosoma brucei brucei* by inhibiting the function of the electron transport system of the mitochondria and along with glycerol, produced total suppression of the energy production, thereby inhibiting in vitro growth of *Trypanosoma brucei*.[29]

Diabetes Metabolic syndrome and Non-alcoholic fatty liver disease (NAFLD)

Thiazolidinediones (TZD), which have insulin sensitizing action, have been recently identified to act on two mitochondrial proteins Mpc2 and Mpc1, which are mitochondrial pyruvate carrier complexes.[30] This complex is responsible for regulation of pyruvate entry into the mitochondria and may be a valid target for insulin sensitization.[30]

A study was done in a mouse model to see the effect of acetyl L carnitine and lipoic acid in non alcoholic fatty liver disease.[31] Treatment with this combination was found to improve hepatic mitochondrial content and size along with improvement of carbamoyl phosphate synthase 1, which is a mitochondrial marker.[31]

Table 1: Various drugs acting on mitochondria.

Diseases	Drugs (article reference number quoted in brackets)	Site of action in mitochondria
Cancer	Paclitaxel[5,6]	Stimulates PTP dependent release of cytochrome c (caspase independent)
	Etoposide[7-11]	Induction of MPT leading to Ca^{2+} dependent swelling of the mitochondria Depolarization of mitochondrial membrane potential
	Vinorelbine[12]	Recruits pro apoptotic protein BIM to mitochondria – apoptosis in interphase
Parkinson's disease	Selegiline and rasagiline[15,16]	Neuroprotection- stimulation of anti apoptotic proteins
Leber's hereditary optic neuropathy	Idebenone[19-24]	Analogue of co enzyme Q10
Angina	Ranolazine[25]	Protects and decreases damage to mitochondrial complex I
Hypertension	Minoxidil[26]	Activates ATP sensitive potassium channels in inner membrane of mitochondria (mitoKATP channel)
Malaria, Pneumocystis carinii	Atovaquone[27,28]	Blocks electron transport chain Collapses mitochondrial membrane potential
Anti parasitic (Trypanosoma brucei)	Ascofuranone[29]	Inhibits function of electron transport chain
Diabetes and metabolic syndrome	Thiazolidinediones[30]	Acts on mitochondrial proteins Mpc2 and Mpc1- target for insulin sensitization
NAFLD (Non alcoholic fatty liver disease)	Acetyl L- carnitine and lipoic acid[31]	improves hepatic mitochondrial content and size with improvement of carbamoyl phosphate synthase 1 (a mitochondrial marker)

PTP: permeability transition pore; MPT: mitochondrial permeability transition; Mpc- mitochondrial pyruvate carrier

Drugs protecting mitochondrial functions

Resveratrol

Resveratrol, a polyphenol occurring naturally in plants like grapevines (*Vitis vinifera*), cranberries (*Vaccinium macrocarpon*) and peanuts (*Arachis hypogaea*), has many properties such as anti-cancer property, anti-diabetic property, cardioprotection and neuroprotection.[32] The postulate put forth by mitochondrial theory of aging is that oxidative stress in mitochondria and the production of free radicals that follows this process is the underlying mechanism of aging.[33]

One of the processes by which resveratrol protects mitochondria is by activation of mitochondrial anti oxidant

systems.[34] Elevated levels of Reactive Oxygen Species (ROS) in mitochondria will result in inhibiting the function of important enzymes such as α-ketoglutarate dehydrogenase and aconitase which play a role in mitochondrial metabolism, and may therefore lead to reduced ATP production.[35]

The cytoprotective effect of resveratrol is due to activation of a transcription factor called Nuclear factor-E_2-related factor-2 (Nrf2).[36] In rodent models of diabetes and aging, activation of the above mentioned Nrf2 dependent pathway helps in promoting cardiovascular and cognitive functioning.[35]

Vitamin E

Well known for its antioxidant property,Vitamin E in high doses was found to restore reduction in mitochondrial respiration and mtNOS (mitochondrial nitric oxide synthase) and complex I and IV activities in rats.[37] Vitamin E was shown to slow down degenerative processes in tissues by reducing production of hydrogen peroxide in mitochondria of rats and its deficiency can lead to ROS overproduction in mitochondria causing tissue damage.[38]

DRUGS CAUSING MITOCHONDRIAL DAMAGE

Nucleoside Reverse Transcriptase Inhibitors (NRTI)

The earliest NRTI 3′- azido-3′-deoxythymidine was shown to inhibit polymerase gamma, which is the enzyme involved in mitochondrial DNA replication in in vitro studies.[39,40] Clinically this mechanism is responsible for the adverse events in patients receiving NRTI therapy.[41] These adverse events comprise a wide spectrum from asymptomatic hyperlactatemia (if compensatory mechanisms are effective) to lactic acidosis, which may be fatal.[41]

Statins

Coenzyme Q10 is a principal factor in mitochondrial respiration and its deficiencies can lead to several neurologic syndromes and myopathies.[42]The synthesis of this compound requires mevalonate, the formation of which is inhibited by statins.[42] Coenzyme Q10 deficiency produced by statins is one of the actions by which these drugs produce myopathy.[42] In addition to coenzyme Q deficiency, inhibition of mevalonate pathway by statins can also cause insufficient production of heme A, which is a member of electron transport chain situated in the inner mitochondrial membrane.[43]

Non Steroidal Anti Inflammatory Drugs (NSAIDS)

One of the mechanisms of diclofenac induced hepatotoxicity is triggering of mitochondrial permeability transition (MPT).[44] When there is opening of MPT pore protons enter the mitochondrial matrix from the intermembrane space, the mitochondrial membrane potential ($\Delta\Psi_m$) is altered unfavourably preventing ATP formation.[45]

The NSAID nimesulide, which is a weak acid uncoupled mitochondria respiration and causes ATP depletion in human hepatoma cells, which was prevented by albumin.[46]

Drugs withdrawn due to mitochondrial toxicity

Mitochondrial toxicity has played an important role in withdrawal of several drugs from the market. A few of those drugs have been discussed below (Table 2).

Fialuridine

In a clinical trial with the drug fialuridine investigated for Hepatitis B infection, seven patients developed hepatic failure, lactic acidosis and pancreatitis, out of which five died.[47] Surprisingly animal studies did not reveal any such adverse effects.[47] These multisystemic adverse effects pointed towards severe mitochondrial damage as one of the causes.[47]

Troglitazone

Troglitazone, an anti diabetic drug, was the first thiazolidinedione licensed for use in type 2 diabetes in the United States in the year 1997, but later withdrawn from market because of liver injury associated with its use.[48] The mechanism of hepatotoxicity could be ascribed to mitochondrial DNA damage caused by this drug.[49]

Perhexilene

In a study done to see the action of the anti anginal drug perhexilene on mitochondria of rats and mice, it was found that this drug uncouples oxidative phosphorylation and reduces beta oxidation of fatty acids.This effect may lead to development of steatosis and pseudoalccoholic liver lesions in humans.[50] This drug was withdrawn from the global market in 1988.[51] However the latest techniques of therapeutic drug monitoring for poor metabolisers of CYP2D6 have paved the way for reintroduction of this drug into the market.[52]

Tacrine

The acetylcholinesterase inhibitor Tacrine, developed for treatment in Alzheimers disease has an adverse effect of hepatotoxicity and has been discontinued for use in the United states because of safety issues.[53] This drug interferes with mitochondrial function by affecting normal activity of complex I and mitochondrial bioenergetics.[54]

Newer compounds in the pipeline

Some novel compounds with action on mitochondria have been discovered and are in clinical trials. Some of them are discussed below.

Table 2: Drugs withdrawn due to mitochondrial toxicity.

Drug	Adverse event caused
Fialuridine[47]	hepatic failure, lactic acidosis and pancreatitis
Troglitazone[48,49]	Hepatotoxicity- mitochondrial DNA damage
Perhexiline[50-52]	Steatosis and pseudoalcoholic liver lesions
Tacrine[53,54]	Hepatotoxicity

Olesoxime

It is a novel neuroprotective compound in the family of cholesterol-oximes which inhibits opening of mitochondrial transition pore by various factors, one of which is oxidative stress.[55] It has the property of enhancing the survival of primary rat motor neurons which are deprived of neurotrophic factors and is being evaluated for its role in the therapy of Amyotrophic lateral sclerosis (ALS) and Spinal muscular Atrophy (SMA).[55]

Lonidamine

Initially developed as a non hormonal male contraceptive drug, it interferes with energy metabolism by its property of inhibition of hexokinase needed for glycolysis and used this property as a treatment for Benign Prostatic Hyperplasia as the prostate relies on glycolysis for energy production.[56] Later this drug was found to possess anti cancer property by interfering with glycolysis and mitochondrial respiration in tumor cells as well as suppressed the activity of mitochondrial pyruvate carrier (MPC), thereby affecting pyruvate uptake in the mitochondria.[57]

Betulinic Acid

A naturally occurring triterpenoid, betulinic acid possesses a wide range of biological properties such as antiretroviral, antimalarial, anti-inflammatory and anti-cancer properties.[58] The cytotoxic action of this drug is due to stimulation of mitochondrial apoptotic pathway in tumor cells.[59] The fact that normal cells possess considerable resistance to its cytotoxic actions makes this drug a promising agent for treatment of cancers.[59]

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