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Targeting the mitochondria to augment myocardial protection

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Summary

The dynamic regulation of the structure, function and turnover of mitochondria is recognized as an immutable control node maintaining cellular integrity and homeostasis. The term 'mitohormesis' has recently been coined to describe the adaptive reprogramming of mitochondrial biology in response to low levels of metabolic substrate deprivation to augment subsequent mitochondrial and cellular tolerance to biological stress [1]. Disruption of these regulatory programs gives rise to cardiovascular and neurodegenerative diseases and augmentation or fine-tuning of these programs may ameliorate mitochondrial and global cellular stress-tolerance. This is in part via the regulation of reactive oxygen species, calcium homeostasis, and in response to caloric restriction, the capacity to augment DNA repair. The objective of this manuscript is to briefly review these regulatory programs and to postulate novel therapeutic approaches with the primary goal of modulating mitochondria to enhance tolerance to cardiac ischemic stress.

Introduction

Mitochondria orchestrate an extensive repertoire of cellular functions and have tissue specific programming to facilitate overall organ function [2]. In the heart, the roles of mitochondria include the generation of energy, the production and metabolism of reactive radical species and the regulation of apoptosis. These functions in turn are exquisitely controlled by regulatory programs governing mitochondrial copy number, functional content and activity, calcium metabolism, stress-tolerance and apoptotic pathways. The identification and characterization of these regulatory programs have promulgated the question of whether these can be modified to adapt mitochondrial function to improve cellular tolerance to biological stress.

In this review article we: 1) describe the innate regulatory pathways driving mitochondrial maintenance of cellular homeostasis, 2) discuss where these programs have been shown to be operational in enhancing stress tolerance in general and in the heart specifically, and 3) to identify current and potential mitochondrial targeted compounds that improve cardiac stress tolerance to prevent or treat ischemic heart disease.

Innate regulatory programs controlling mitochondrial plasticity

Mitochondrial biogenesis, the molecular control of mitochondrial turnover, content and number exquisitely coordinates diverse homeostatic demands via communication between the mitochondrial and nuclear genomes. The regulatory proteins and signaling pathways

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conducting this inter-genomic control has been reviewed recently [3,4]. The functional importance of mitochondrial biogenesis in maintaining cardiac homeostasis is evident in that the genetic ablation of master regulators of mitochondrial biogenesis, i.e. the peroxisome proliferator activated receptor γ coactivator 1 α and β (PGC1α/β) diminish cardiac adaptation to adrenergic stimulation and pressure-overload [5-7]. The disruption of downstream cognate transcription factors including the three major peroxisome proliferator activated receptor (PPAR) subtypes, also leads to cardiac contractile dysfunction and an enhanced susceptibly to oxidative damage [8-10]. Furthermore, the modest induction of transcription factor A of mitochondria (TFAM) evokes protection against ischemia induced heart failure [11]. However, excessive activation of this program becomes pathological as is shown by the generation of an over-abundance of mitochondria resulting in cardiomyopathy following sustained overexpression of murine heart PGC1α [12]. Moreover, chronic overexpression of PPARα in the heart blunts contractile recovery in response to ischemic stress [13]. An additional level of regulation of mitochondrial homeostasis is the molecular control of mitochondrial fusion and division (reviewed [14]) with unpublished data showing that enhancing mitochondrial fusion augments cardiomyocyte ischemia-tolerance [15]. Biological compounds that activate the mitochondrial biogenesis program will be discussed as putative modulators of ischemia-tolerance.

Caloric restriction orchestrated mitochondrial stress response

Hormesis is defined as the activation of cellular protective and reparative properties induced by mild physiologic stress. Caloric restriction is considered an hormetic process where chronic mild starvation enhances cellular DNA repair capacity and antioxidant defenses [16,17] and upregulates the mitochondrial biogenesis regulatory program [18]. Although the cardiac mitochondrial regulatory perturbations in response to caloric restriction have not been well characterized, short-term caloric restriction confers resistance to cardiac ischemia-reperfusion [19]. A candidate regulatory protein that may orchestrate this cardioprotective effect is the nutrient sensor protein sirt1. This NAD-dependent deacetylase enhances stress tolerance and lifespan extension during caloric restriction [20]. Accordingly sirt1 has been shown to attenuate constitutive and H_2O_2 mediated apoptosis in cardiomyocytes [21] and to protect the intact heart against paraquat mediated oxidative stress [22]. While this biology requires more extensive investigation, caloric-restriction mimetics may be candidates to blunt ischemia-reperfusion injury.

Ischemic preconditioning identifies mitochondrial targets to enhance ischemiareperfusion tolerance

A second stress-activated program operational in the heart and extensively investigated is the biological phenomenon termed ischemic preconditioning [23]. Here too, the regulation of mitochondria has been implicated in augmenting tolerance to ischemia-reperfusion. The preconditioning-induced mitochondrial perturbations identified to date include upregulation of antioxidant defense mechanisms including via the transient inhibition of mitochondrial respiration [24], via transient mitochondrial uncoupling [25,26] and by upregulation of antioxidant enzymes [27]. Furthermore, ischemic preconditioning reduces the susceptibility to mitochondrial permeability transition [15]. In the later part of this review we will discuss compounds that can mimic these mitochondrial effects as potential cardioprotective agents. The proposed mechanism enhancing mitochondrial ischemia tolerance in response to caloric restriction and preconditioning are schematized in figure 1.

Potential mitochondrial modulators to ameliorate ischemic injury

The mitochondrial adaptations to caloric restriction and ischemic preconditioning identify potential targets to explore as therapeutic modulators of ischemia-tolerance. In the remainder of this review we will review compounds with specific focus on potential caloric restriction mimetics, a class of compounds that may induce mitochondrial biogenesis, a novel anion known to transiently inhibit mitochondrial respiration under ischemia and a mitochondrial targeted antioxidant. Mitochondrial permeability inhibitors which have recently been reviewed are not discussed [23].

Resveratrol – a potential caloric restriction mimetic

The plant-derived polyphenol resveratrol (3,5,4'-trihydroxystilbene) is enriched in red wine and functions as a caloric restriction mimetic via upregulation of sirt1 and AMP-activated kinase (AMPK) [28-30]. Additionally it exhibits antioxidant properties [31] and upregulates the mitochondrial biogenesis program [28]. Signaling intermediates induced by this putative 'mitohormetic' compound have been identified [32,33]. Consistent with its known pleiotropic effects resveratrol administration confers protection against cardiac ischemia-reperfusion injury [31,34,35].

As a therapeutic agent, resveratrol has limitations in that it has a short initial half-life and limited in-vivo bioavailability [31]. To counter this, numerous investigators are exploring compounds to restrict its catabolism. Furthermore, to differentiate the cardioprotective properties from the pleiotropic effects of resveratrol, small molecules that may directly activate, for example, sirt1 are being actively pursued [36]. Once identified, the direct cardiac-tolerance effects of activation of sirt1 activators would need to be validated.

AMP-Kinase activating compounds and mitochondrial biogenesis

The activation of the fuel sensor AMPK by exercise or by the AMPK activators AICAR (5-aminoimidazole-4-carboxamide 1β-D-ribofuranoside) and β-guanidinopropionic acid enhances mitochondrial function and biogenesis in skeletal muscle [37,38]. With respect to AICAR, this is shown to be due to the direct upregulation of PGC-1α [39-41] and to the enhanced expression of mitochondrial proteins cytochrome c, UCP-3, and citrate synthase [42,43]. In the heart, ischemia increases AMPK activation [44], and loss of AMPK exacerbates ischemia-reperfusion injury [45]. However, whether the activation of AMPK augments mitochondrial biogenesis in the heart has not been established. Conversely, the genetic depletion of AMPKα2 isoform alters cardiac mitochondrial ultrastructure and disrupts complex I of the electron transfer chain [46]. Cumulatively these data suggest that the activation of AMPK may induce ameliorative effects on mitochondrial biology to enhance ischemia tolerance.

These cardioprotective effects of AMPK activation are likely not exclusively due to mitochondrial manipulations as activation of this fuel-sensing kinase evokes multiple additional metabolic effects (reviewed [47]). Furthermore, the use of AICAR as a cardiac therapeutic target is limited in that it promotes bradycardia and hypoglycemia [48]. Current therapeutic agents that indirectly activate AMPK include the biguanides and the thiazolidinediones [49]. Interestingly, both these anti-diabetic drugs have been shown to augment mitochondrial biogenesis [50,51] and in separate studies, to confer protection against cardiac ischemia [52,53]. As above, whether these effects are directly due to modulation of mitochondrial function in the heart is not established. Nevertheless, several drug discovery programs are pursuing more specific and potent AMPK activators [48] and with the development of these compounds, the capacity to directly link their activation with the modulation of mitochondria and cardiac tolerance can be explored.

Nitrite - a novel ischemia-inducible electron transfer chain inhibitor

Chronic uncoupling of oxidative phosphorylation or inhibition of the electron chain transfer would be incompatible with sustained ATP production essential for cardiac contraction. However, in the context of ischemia-reperfusion, acute uncoupled respiration and inhibition of complex I of the electron transfer chain (ETC) inhibit mitochondrial reactive oxygen species production, via reduced electron dissociation from the ETC (reviewed [54]) and via reduced electron flow through complex III resulting in a reduction in superoxide generation [55], respectively. A pharmacologic agent that could dynamically replicate either of these perturbations exclusively under ischemia-reperfusion conditions would introduce a novel therapeutic approach.

In this respect, the nitrite anion (NO_2^-) is an intriguing 'candidate' in that it is reduced to nitric oxide (NO), a known cardioprotective compound [56] and an inhibitor of mitochondrial electron transfer [57], primarily at low tissue pH and under hypoxic conditions. Under these conditions nitrite is either directly reduced to NO by disproportionation and/or by the enzymatic action of heme-containing proteins, including xanthine oxidoreductase, electron transfer proteins, deoxyhemoglobin, and dexoymyoglobin [58]. Indeed, administration of nitrite in preclinical studies confers protection against ischemia-reperfusion injury [59] in parallel with a reduction in post ischemic reactive oxygen species production and by reducing the activation of the MPTP [57]. In the latter study, it was shown that nitrite does not affect mitochondrial respiration under normoxic conditions, but rather inhibits complex I of the electron transfer chain in response to hypoxia and reoxygenation [57]. From a therapeutic perspective, the most exciting aspects of this study are that the administration of nitrite could precede the ischemic injury by as much as 24 hours and that this anion could be administered orally [57]. Pilot studies in human subjects are now being planned.

MitoQ - a mitochondrial-targeted antioxidant

Although the benefit of therapeutic antioxidants to limit oxidative damage during ischemic injury has not been realized, given the mitochondria's role as both source and target of ROS the use of the novel mitochondria-targeted antioxidants has gained interest (Reviewed [60]). Mitochondrial targeting is feasible by conjugating an antioxidant to a lipophilic cation. This exploits the high inner mitochondrial membrane potential enabling mitochondrial accumulation of this cation-conjugated target at 100−1000 times higher concentration than in cytoplasm [61,62]. MitoQ, based on the endogenous mitochondrial ubiquinone coenzyme Q is such a compoung. It has a redox chemistry closely regulated by the ETC possibly allowing MitoQ to simultaneously decrease oxidative damage and upregulate respiration.

In vivo animal studies have shown that MitoQ decreases ROS, apoptosis and ischemiareperfusion cardiac injury in conjunction with improved respiratory coupling and increased complex I and aconitase activities [62]. MitoQ has been proven to be well tolerated and toxic only at very high concentrations [63]. Trials are underway for neurological disorders, but the impact of this agent on human cardiac disease remains to be tested.

Conclusions

Mitochondrial plasticity, under both acute and chronic regulation, is increasingly recognized as integral to cellular and tissue tolerance of ischemic stress. Chronic modulation of mitochondrial content and function via the principle of mitohormesis underlies the protective effect of caloric restriction mimetics. Acutely, alteration of electron flow and inhibition of reactive species production remain attractive targets for cardioprotection. Importantly, better biologic understanding has led to therapeutics with increased specificity of action. This is illustrated by the action of nitrite to function as a putative dynamic regulator of electron flux,

specifically under conditions of low oxygen and acidosis. This anion may potentially represent the first truly ischemia-activated agent. Exploiting mitochondrial biology has also enabled the development of mitochondrial-targeting agents such as antioxidants which may ultimately realize their long proposed benefits. The true impact of these developments on human cardiovascular health awaits further clinical study. Finally, the proposed compounds and their mechanisms of actions discussed in this review are shown schematically in figure 2.

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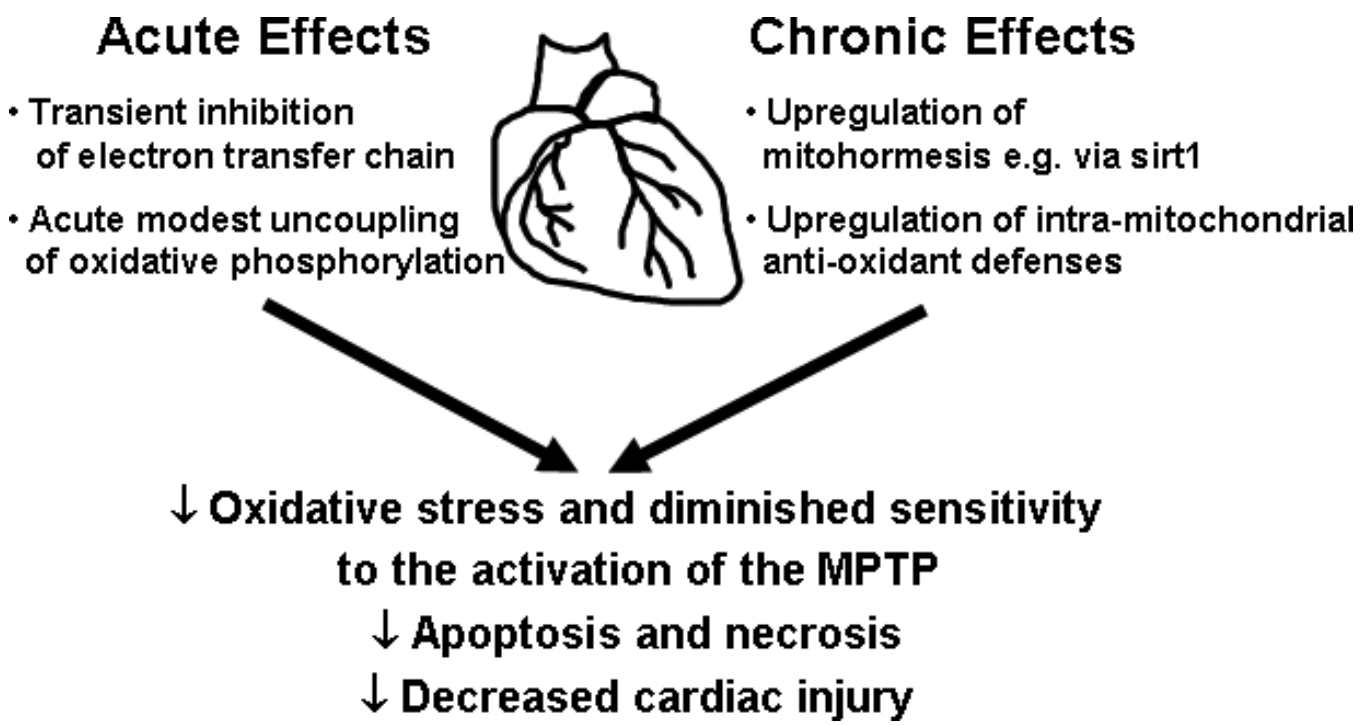

Figure 1.
Schematic of modulations of mitochondria to augment cardiac ischemia-tolerance

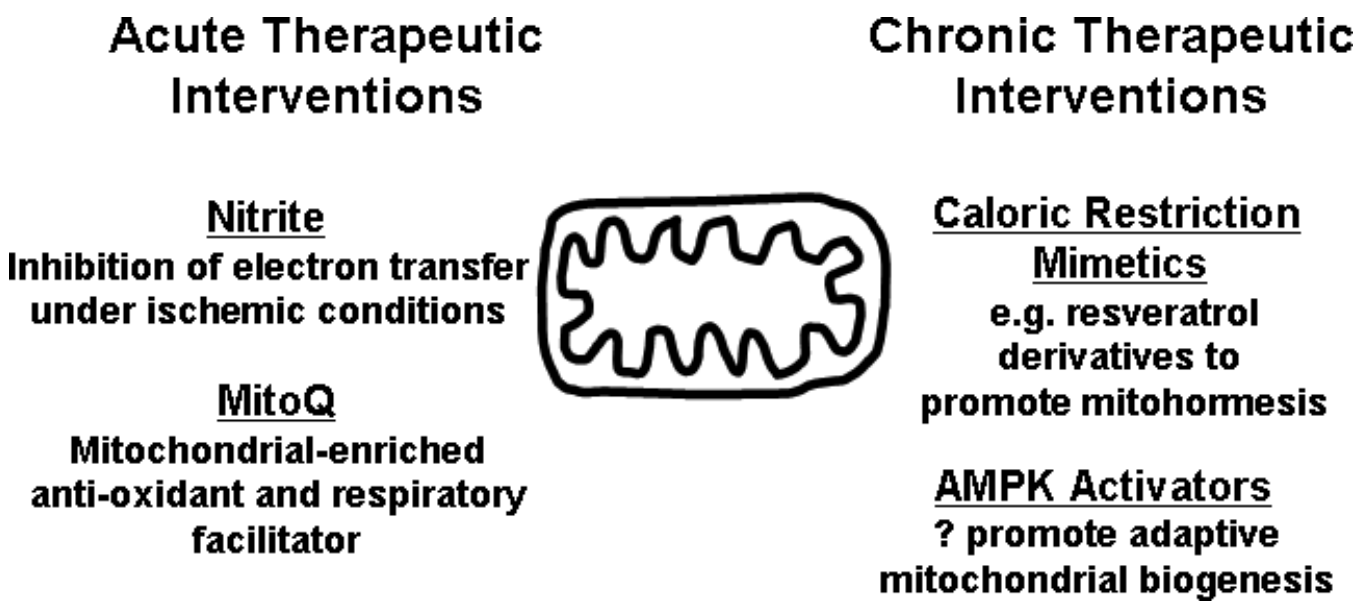

Figure 2.
Mitochondrial directed therapeutic agents to enhance cardiac ischemia-tolerance