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Contribution of mitochondrial oxidative stress to hypertension

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Abstract

Purpose of review—In 1954 Harman proposed the free radical theory of aging, and in 1972 he suggested that mitochondria are both the source and the victim of toxic free radicals. Interestingly, hypertension is age-associated disease and clinical data show that by age 70, 70% of the population has hypertension and this is accompanied by oxidative stress. Antioxidant therapy however is not currently available and common antioxidants like ascorbate and vitamin E are ineffective in preventing hypertension. The present review focuses on molecular mechanisms of mitochondrial oxidative stress and therapeutic potential of targeting mitochondria in hypertension.

Recent findings—In the past several years, we have shown that the mitochondria become dysfunctional in hypertension and have defined novel role of mitochondrial superoxide radicals in this disease. We have shown that genetic manipulation of mitochondrial antioxidant enzyme superoxide dismutase (SOD2) affects blood pressure and have developed mitochondria-targeted therapies such as SOD2 mimetics that effectively lower blood pressure. The specific mechanism of mitochondrial oxidative stress in hypertension, however, remains unclear. Recent animal and clinical studies have demonstrated several hormonal, metabolic, inflammatory, and environmental pathways contributing to mitochondrial dysfunction and oxidative stress.

Summary—Nutritional supplements, calorie restriction, and life style change are the most effective preventive strategies to improve mitochondrial function and reduce mitochondrial oxidative stress. Aging associated mitochondrial dysfunction, however, reduces efficacy of these strategies. Therefore, we propose that new classes of mitochondria-targeted antioxidants can provide high therapeutic potential to improve endothelial function and reduce hypertension.

Keywords

Mitochondria; Hypertension; oxidative stress; reactive oxygen species; antioxidants

INTRODUCTION

Hypertension is a multifactorial disorder involving perturbations of the vasculature, the kidney and the central nervous system (1). Despite treatment with multiple drugs, 37% of hypertensive patients remains hypertensive (2), likely due to the mechanisms contributing to blood pressure elevation that are not affected by current treatments. Human hypertension is

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Conflicts of interest

There are no conflicts of interest.

associated with reduced activity of antioxidant enzymes and increased production of reactive oxygen species (ROS: $O_2^{\bullet-}$ and H_2O_2) leading to oxidative stress as measured by lipid and DNA oxidation (Figure 1) (3, 4). Indeed, in almost all experimental models of hypertension ROS are increased in multiple organs, including critical centers of the brain, the vasculature, and the kidney. In the brain, ROS promote neuronal firing, ultimately increasing sympathetic outflow (5, 6). In the kidney, ROS act in multiple sites to promote sodium resorption and volume retention (7). In the vasculature ROS promote vasoconstriction and remodeling, increasing systemic vascular resistance (8). Our group has revealed several sources of ROS contributing to hypertension, including the NADPH oxidase, uncoupled nitric oxide synthase, and the mitochondria (9**) and defined their interaction (10, 11). Meanwhile, antioxidant therapy is not currently available, and common antioxidants like ascorbate and vitamin E are ineffective in preventing cardiovascular diseases and hypertension (12), since these agents likely do not reach important sites of ROS production such as mitochondria.

REGULATION OF MITOCHONDRIAL ROS

The major biological function of mitochondria is ATP synthesis (13). This process is based on transfer of electrons through the mitochondrial respiratory chain coupled with transporting protons (H^+) from the matrix to the intermembrane space to generate the proton motive force which is used for conversion of ADP to ATP. Several sites of the electron transport chain "leak" electrons to O_2 creating $O_2^{\bullet-}$ (14, 15). This is not a "spontaneous" process, and the production of mitochondrial ROS is highly regulated (9**, 10). It strongly depends on the pH gradient across the inner membrane (16), activation of mitochondrial ATP-sensitive potassium channels ($mitoK^+_{ATP}$) (17, 18), and opening of mitochondrial permeability transition pore (mPTP) (19, 20). Mitochondrial $O_2^{\bullet-}$ is rapidly converted to H_2O_2 by SOD2 (21, 22), and H_2O_2 is a neutral molecule which easily leaves mitochondria. We have previously shown that activation of NADPH oxidases increases the production of mitochondrial ROS and vice versa: increase in mitochondrial ROS activates NADPH oxidases (19, 23). Production of mitochondrial ROS, therefore, is redox-dependent and represents an ongoing feed-forward cycle (10). It is recognized that mitochondrial ROS play an important physiological function (24); however, excessive stimulation of mitochondria leads to ROS overproduction and depletion of antioxidants resulting in imbalance between oxidant production and antioxidant defense system which constitutes an oxidative stress (Figure 2).

SIRTUIN 3 AND MITOCHONDRIAL SUPEROXIDE DISMUTASE (SOD2)

Mitochondrial SOD2 is a key antioxidant enzyme and acetylation represents a major post-translational regulation of SOD2 activity. SOD2 in vivo is activated by Sirtuin 3 mediated deacetylation of specific lysine residues (25). NAD^+-dependent mitochondrial Sirtuin 3 (Sirt3) acts as a metabolic sensor, using intracellular metabolites such as NAD^+ and acetyl-CoA to modulate mitochondrial function to match nutrient supply (Figure 3) (26). Access of Acetyl-CoA leads to SOD2 hyperacetylation resulting in SOD2 inactivation, and deacetylation by Sirt3 restores SOD2 activity (27). The profound increase of hypertension with age is associated with the decline of both mitochondrial energy metabolism (28) and the NAD^+ dependent deacetylase activity (29). Sirt3 is a nuclear-encoded protein, however,

the majority of Sirt3 translocates to mitochondria (29). Clinical studies have shown that Sirt3 expression declines by 40% by age 65 paralleling the increased incidence of hypertension (28, 30). Angiotensin II and inflammation also mediate the decline in Sirt3 activity (31). Interestingly, SOD2 expression is not changed with age but the activity of Sirt3 and SOD2 are diminished (32) suggesting that SOD2 acetylation contributes to hypertension. Indeed, we have shown that SOD2 overexpression attenuates hypertension (23), while SOD2 depletion enhances oxidative stress and hypertension.

There are several genetic and metabolic factors which affect Sirt3 expression and activity. Bellinzi et al. have discovered a variable number tandem repeat (VNTR) polymorphism which has an allele-specific enhancer activity and this activity is virtually absent in men older than 90 years (33). Authors suggested that Sirt3 underexpression can be detrimental for longevity as it occurs in animal models (34). Dransfeld et al. have recently identified two non-synonymous human SIRT3 SNPs and evaluated their impact on SIRT3 activity and stability (35). It is interesting that multiple risk factors for hypertension are associated with the reduced Sirt3 expression and activity. For example, Sirt3 activity is metabolically downregulated by increased Acetyl-CoA and reduced NAD^+ in metabolic syndrome, hyperlipidemia, diabetes and sedentary lifestyle while aging and smoking reduces Sirt3 expression (Figure 3) (30, 36*). It has been suggested that dietary supplementation of Sirt3 activating compounds such as resveratrol can be beneficial (37, 38). Resveratrol supplementation reduced renal inflammation and attenuated hypertension in the animal models (39*); however, recent clinical studies showed mixed results of resveratrol supplementation in cardiovascular disease and human hypertension (40, 41).

AGING AND MITOCHONDRIAL IMPAIRMENT

Silencing information regulator 2 (SIR2) extends lifespan in yeast, worms, and flies (42), and sirtuins are SIR2 homologs in mammals (43). SIRT3 is suppressed with aging and SIRT3 upregulation in aged hematopoietic stem cells improves their regenerative capacity (32). Therefore, Sirt3 is one of the potential candidates for age-associated development of cardiovascular diseases. Indeed, Sirt3 expression declines by 40% by age 65 paralleling the increased incidence of hypertension (30). Sirt3 activation of mitochondrial metabolism by deacetylation of key Krebs cycle enzymes, promotes fatty acid β-oxidation, activates complex I, improves antioxidant defense by activation of NADPH producing isocitrate dehydrogenase and increasing SOD2 activity (27, 44). There is compelling evidence for accumulation of oxidative damage to specific mitochondrial proteins which leads to the progressive mitochondrial dysfunction with aging (45). The role age-associated mitochondrial oxidative stress in hypertension was highlighted in the studies of mice deficient in mitochondrial superoxide dismutase ($SOD2^{-/+}$) which have age-associated hypertension and increased sensitivity to salt (46). Recent studies further support the role of mitochondrial oxidative stress in the aging which depresses respiratory function and contribute to muscle atrophy (47). The early dysfunction appears to be reversible based on improved mitochondrial function and elevated mitochondrial gene expression after exercise training (48).

ANGIOTENSIN II AND MITOCHONDRIAL DYSFUNCTION

Interestingly, angiotensin-converting enzyme inhibitor enalapril and angiotensin II type I receptor (AT1R) blocker losartan attenuate age-associated mitochondrial dysfunction (49). Angiotensin II stimulates ROS production by non-phagocytic NADPH oxidases such as Nox1 and Nox2. We have investigated the potential cross talk between mitochondria and NADPH oxidases (10). It was found that depletion of p22phox and Nox1 subunits of NADPH oxidases in endothelial cells completely prevented angiotensin II induced mitochondrial oxidative stress (9**, 19). Furthermore, scavenging of mitochondrial ROS by acute treatments with mitochondria-targeted antioxidants mitoTEMPO and mitoEbselen attenuated NADPH oxidase activity and reduced $O_2^{\bullet-}$ production in the cytoplasm (9**, 50). These data demonstrate redox-dependent cross-talk between cytoplsamic Nox2 and mitochondrial ROS in endothelial cells. Other cell types, however, have different Nox isoforms. Vascular smooth muscle cells, for example, express Nox1 which is upregulated by angiotensin II (51, 52) and, therefore, Nox1 can play an important role in cross-talk between mitochondrial ROS and NADPH oxidase in vascular smooth muscle cells. Indeed, both angiotensin II and mitoK^+_{ATP} activator diazoxide stimulated mitochondrial ROS and NADPH oxidase in rat vascular smooth muscle cells in vitro and in rat aorta (53).

The cross-talk between NADPH oxidases and mitochondrial ROS is bi-directional. Angiotensin II activates NADPH oxidases via AT1R receptor, while expression of AT1R is redox dependent and thereby overproduction of mitochondrial ROS may enhance stimulation of AT1R mediated pathways (11). NADPH oxidases produce $O_2^{\bullet-}$ and H_2O_2 which increase intracellular Ca^{2+} and stimulate redox dependent mitoK^+_{ATP} and PKCε (Figure 4) which triggers Ca^{2+} and redox induced production of mitochondrial ROS (18, 50, 54). Activation of c-Src is redox sensitive and is stimulated by H_2O_2 (55), which appears to represent a feed-forward mechanism, whereby mitochondrial H_2O_2 amplifies NADPH oxidase activity (9**). Mitochondria apparently regulate both expression (56) and activity of NADPH oxidases (57). Partial depolarization of mitochondrial membrane potential reduces Ca^{2+} uptake by mitochondrial uniporter and increases Ca^{2+} dependent activation of NADPH oxidases (57), while depletion of SOD2 results in increase of basal and stimulated vascular NADPH oxidase activity (23). Therefore, overproduction of mitochondrial ROS may result in overstimulation of cytoplasmic NADPH oxidases and dysregulation of cellular signaling leading to the development of vicious cycle of oxidative stress (23).

CALORIE RESTRICTION AND MITOCHONDRIAL ANTIOXIDANTS

It has been previously shown that calorie restriction attenuates hypertension in rat models (58); however, the exact mechanisms and therapeutic potential of this intervention is not clear. It has been suggested that calorie restriction activates AMPK pathway which improves NO synthase phosphorylation and endothelial function (58). Calorie restriction increases expression of endothelial and neuronal NO synthase and enhances NO-mediated mitochondrial biogenesis (59, 60). Other groups have shown that calorie restriction (25) increases Sirt3 expression and activity which may suggest that increased Sirt3 activity may reduce hypertension. Recent clinical studies showed substantial decrease in systolic blood pressure by 20 mm Hg in subjects following one year of calorie restriction (61) which can be mediated by a number of pathways. One potential mechanism may include upregulation

of Sirt3 by calorie restriction and Sirt3 stimulated mitochondrial antioxidant defense system (Figure 5) (62). The mitochondrial NAD^+-dependent Sirt3 is upregulated in response to fasting and calorie restriction while high-fat diet downregulates Sirt3 leading to mitochondrial protein hyperacetylation and oxidative stress (63).

Calorie restriction activates Sirt1 and Sirt3, therefore, new sirtuin activators has been developed as calorie restriction mimetics which can be beneficial in age-related disorders (64). Indeed, preclinical and clinical studies support the role of sirtuin activator resveratrol in the treatment of cardiovascular diseases (65**). Furthermore, the enzymatic activities of isocitrate dehydrogenase 2, glutathione peroxidase, and SOD2, as well as deacetylation of SOD2 were increased by resveratrol treatment in endothelial cells supporting the effect of resveratrol through Sirt3 signaling pathway (66).

PHYSICAL ACTIVITY AND MITOCHONDRIA

Physical activity affects mitochondrial function through multiple pathways which include shear stress stimulation of NO-mediated mitochondrial biogenesis (60, 67), metabolic regulations (68**), increased antioxidant expression (69), and NAD^+ dependent Sirt3 activation (70). Endurance exercise attenuates age-associated reduction in Sirt3 expression and improved mitochondrial function (Figure 5) (28). It is important to note that excessive exercise can induce mitochondrial damage followed by excessive ROS production, NFκB activation, and proinflammatory cytokines formation (71). Moreover, high-intensity exercise in elderly subjects does not reverse age-related mitochondrial damage and dysfunction but can contribute to further alteration of mitochondrial morphology (71). It is clear that regular exercise reduces mitochondrial oxidative stress and improves mitochondrial function, however, high-intensity exercise should be avoided, particularly in elderly subjects.

SMOKING AND MITOCHONDRIAL OXIDATIVE STRESS

Smoking is one of the major risk factors for development of hypertension (72). Smoking increases blood pressure both in normotensive and hypertensive subjects (73, 74); however, smoking cessation success is very limited (7%) (75, 76), and risk for cardiovascular diseases remains elevated long after quitting smoking (77, 78). Smoking increases oxidative stress (79) and causes mitochondrial dysfunction (80, 81). Cigarette smoke increases $O_2^{\bullet-}$ production (82) and reduces Sirt3 levels (36*) which can further exacerbate mitochondrial oxidative stress. The precise mechanisms of smoking induced mitochondrial oxidative stress remain elusive.

Clinical studies showed that accumulation of lipid oxidation product malondialdehyde in blood plasma of smokers was increased by 2.5-fold while activity of major antioxidant enzymes catalase, superoxide dismutase and glutathione peroxidase were significantly reduced (83). This leads to oxidation of cysteine and glutathione, and the level of reduced glutathione is diminished in kidney by 2-fold in mice exposed to cigarette smoke for four days (84). The resultant alteration in the thiol redox status impairs cellular redox signaling and can contribute to cellular and mitochondrial dysfunction. Indeed, smoking a single cigarette rapidly reduces endothelial nitric oxide production and significantly diminishes blood plasma antioxidants (85). It has been proposed that cigarette smoke induces $O_2^{\bullet-}$

production in endothelial cells leading to NO inactivation and NO synthase uncoupling (86). Finally, cigarette smoke induces metabolic reprograming in mitochondria which contributes to cancer development (81, 87). These metabolic alterations are associated with NADH accumulation (81) resulting in increased mitochondrial $O_2^{\bullet}$ and reduced SOD2 activity (88). Interestingly, hypertensive patients with smoking have significantly reduced responses to common classes of antihypertensive drugs potentially due to metabolic interference between cigarette smoking and drugs (72), therefore, new classes of antihypertensive agents could add to the currently available therapeutic armamentarium to improve treatment of hypertension. It is possible that new mitochondria-targeted therapeutic approaches can be useful in treatment of subjects with history of smoking.

TARGETING MITOCHONDRIAL OXIDATIVE STRESS IN HYPERTENSION

We have developed a mitochondria-targeted SOD2 mimetic, mitoTEMPO, by conjugating the lipophilic triphenylphosphonium cation to an antioxidant moiety SOD mimetic TEMPO (23). Our data indicate that mitoTEMPO accumulates several-hundredfold within mitochondria, likely due to its positive charge and driven by the mitochondrial membrane potential. This markedly enhances scavenging of mitochondrial $O_2^{\bullet}$ and provides protection of mitochondrial and cellular function from $O_2^{\bullet}$ overproduction (Figure 5). Inhibition of mitochondrial oxidative stress with mitoTEMPO supplementation attenuates endothelial oxidative stress, restores NO• production, improves endothelium-dependent vasodilatation and reduces blood pressure in angiotensin II and DOCA-salt models of hypertension (23).

We have recently tested hypothesis that mitochondrial H_2O_2 stimulates mitochondrial $O_2^{\bullet}$ production and contributes to vicious cycle of oxidative stress which can be interrupted at the mitochondrial site by mitochondria targeted H_2O_2 scavenger mitoEbselen (9**). Indeed, supplementation of endothelial cells with mitoEbselen abolished angiotensin II-induced mitochondrial $O_2^{\bullet}$ production and acute treatment with mitoEbselen after onset of mitochondrial oxidative stress reduced mitochondrial $O_2^{\bullet}$ and diminished cytoplasmic $O_2^{\bullet}$ production by NADPH oxidases (9**, 50). Furthermore, treatment of hypertensive mice with mitoEbselen after onset of angiotensin II-induced hypertension diminished vascular oxidative stress and significantly reduced blood pressure (9**). Despite the fact that mitochondria-targeted scavengers of $O_2^{\bullet}$ and H_2O_2 have shown significant antihypertensive activity additional translational studies are required in order to move mitochondria-targeted antioxidants from bench to the bedside.

There are two currently available mitochondria directed strategies: supplementation with mitochondrial co-factor ubiquinone (CoQ_{10}) and treatment with cardiolipin-protective compound bendavia. Ubiquinone is reduced in hypertension, and CoQ_{10} supplementation has an antihypertensive effect (Figure 5) (89). It has been suggested that ubiquinone acts as mitochondrial antioxidant. Our studies, however, do not support significant free radical scavenging by Ubiquinone (90). Ubiquinone primarily functions as electron carrier and it is a critical cofactor in the enzymatic electron transfer in mitochondrial electron transfer chain. Therefore, Ubiquinone can potentially improve oxidative phosphorylation and reduce “electron leakage” in mitochondria. Bendavia (Stealth BioTherapeutics) is a candidate drug that inhibits cytochrome c/cardiolipin peroxidase activity (91). As a result, Bendavia

protects the structure of mitochondrial cristae and promotes oxidative phosphorylation (92). In preclinical studies Bendavia reduced renal and cardiac ischemic injury, mitigated microvascular rarefaction and fibrosis, prevented acute kidney injury and improved postinfarction cardiac function (93**-95). Multiple Phase 1 and phase 2 trials studying Bendavia in mitochondrial conditions have found that the drug is well tolerated.

CONCLUSION

In the past decade it has become clear that mitochondrial oxidative stress contributes to hypertension. Several mitochondria-targeted strategies have been developed. Meanwhile, there are still many questions left unanswered: the precise molecular mechanisms leading to mitochondrial oxidative stress in hypertension and end organ dysfunction remain unclear; the response of specific cells and tissue to mitochondria-targeted treatments is not known; the therapeutic potential of targeting mitochondrial regulators of ROS production and antioxidant activity has not been validated. Additional studies are required to address these questions. In the interim, careful attention to preventive strategies and lifestyle modification must be used. The strengths and weaknesses of each approach will help clinicians and researchers to determine which measures are best for each particular situation.

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KEY POINTS

- Hypertension is associated with increased production of mitochondrial superoxide and reduced activity of antioxidant defense system which contributes to the pathogenesis of hypertension and end organ dysfunction;
- Several risk factors for hypertension such as aging, smoking and metabolic conditions increases mitochondrial oxidative stress and lifestyle modification reduces mitochondrial dysfunction and attenuate hypertension.
- Future studies must be directed to determine the precise molecular mechanisms of mitochondrial oxidative stress in hypertension and validate the therapeutic potential different of mitochondria-targeted strategies.

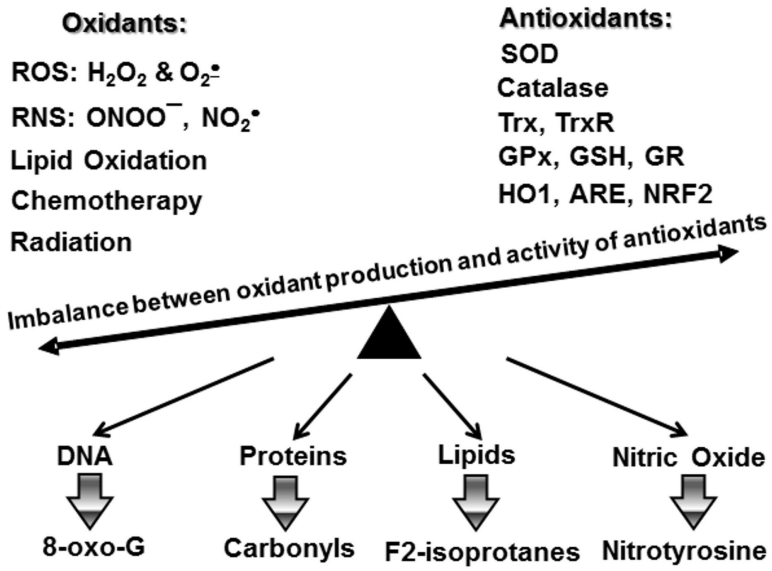

Figure 1.

Oxidative stress is an imbalance between oxidant production and activity of antioxidant system leading to oxidation of multiple biological targets such as DNA, proteins, lipids and nitric oxide which can be followed by accumulation of markers of oxidative stress.

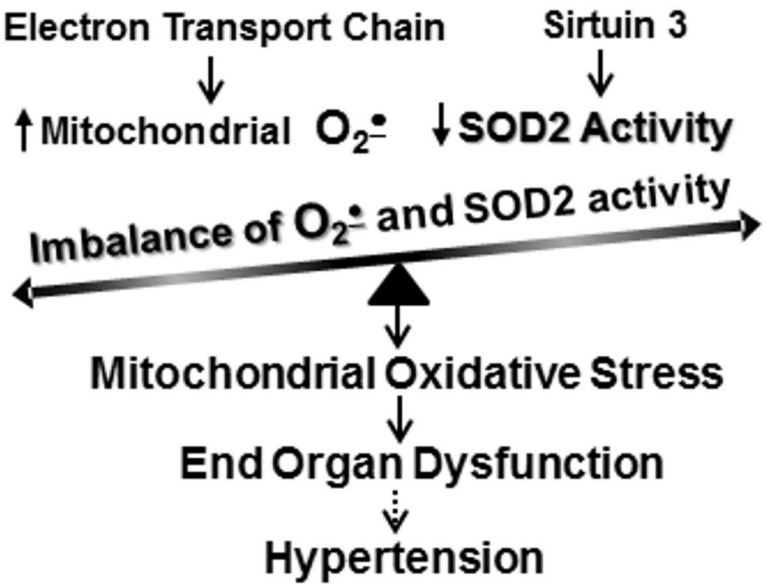

Figure 2.

Overproduction of mitochondrial superoxide and reduced SOD2 activity leads to mitochondrial oxidative stress which contributes to end organ dysfunction and hypertension.

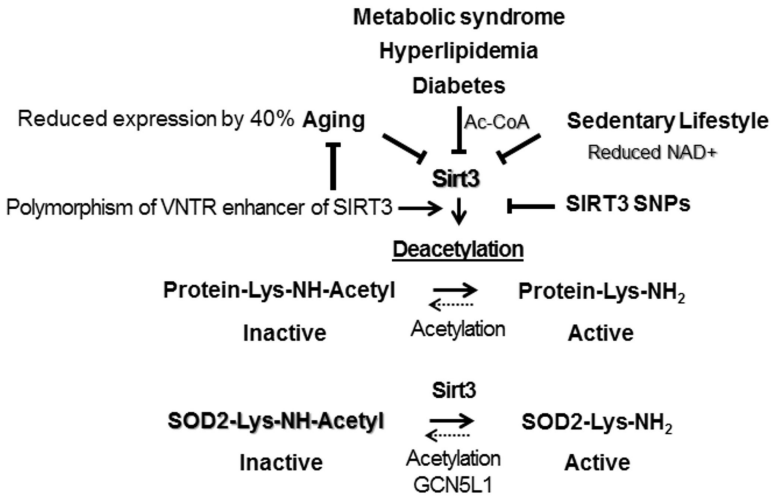

Figure 3.

Critical role of Sirt3 in regulation of mitochondrial metabolism and activation of mitochondrial superoxide dismutase (SOD2). Aging, metabolic conditions and lifestyle alterations reduce Sirt3 activity and increase SOD2 acetylation leading to SOD2 inactivation which contributes to mitochondrial oxidative stress.

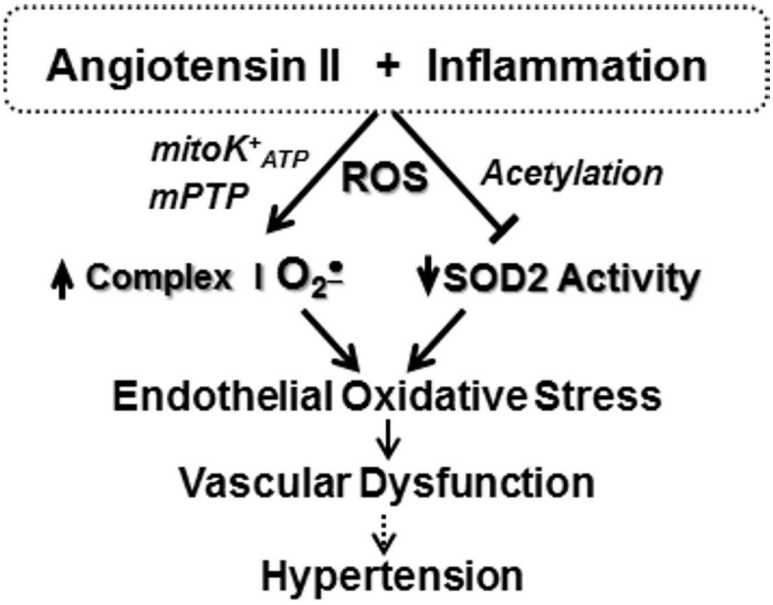

Figure 4.

Angiotensin II and inflammation increases ROS production by NADPH oxidases which lead to opening of mitochondrial redox sensitive mitochondrial channels (mPTP and mitoK$^+_{ATP}$) and increased acetylation of mitochondrial enzymes. In endothelial cells this stimulates superoxide production by complex I and reduces SOD2 activity leading to endothelial oxidative stress, impaired vasodilatation and increased hypertension.

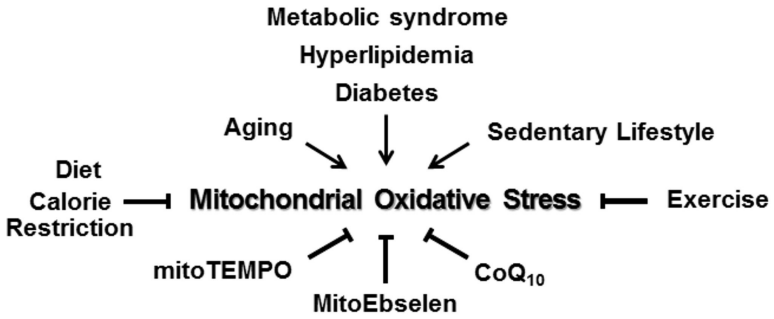

Figure 5.

Multiple risk factors for hypertension such as aging, metabolic conditions and smoking and sedentary lifestyle increase mitochondrial oxidative stress. This can be reduced by diet, calorie restriction, exercise, co-enzyme CoQ10 supplementation or directly with mitochondria-targeted antioxidants such as mitoTEMPO and mitoEbselen.