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MITOCHONDRIAL FUNCTION IN HYPOXIC ISCHEMIC INJURY AND INFLUENCE OF AGING

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Abstract

Mitochondria are a major target in hypoxic/ischemic injury. Mitochondrial impairment increases with age leading to dysregulation of molecular pathways linked to mitochondria. The perturbation of mitochondrial homeostasis and cellular energetics worsens outcome following hypoxic-ischemic insults in elderly individuals. In response to acute injury conditions, cellular machinery relies on rapid adaptations by modulating posttranslational modifications. Therefore, post-translational regulation of molecular mediators such as hypoxia-inducible factor 1α (HIF-1α), peroxisome proliferator-activated receptor γ coactivator α (PGC-1α), c-MYC, SIRT1 and AMPK play a critical role in the control of the glycolytic-mitochondrial energy axis in response to hypoxic-ischemic conditions. The deficiency of oxygen and nutrients leads to decreased energetic reliance on mitochondria, promoting glycolysis. The combination of pseudohypoxia, declining autophagy, and dysregulation of stress responses with aging adds to impaired host response to hypoxic-ischemic injury. Furthermore, intermitochondrial signal propagation and tissue wide oscillations in mitochondrial metabolism in response to oxidative stress are emerging as vital to cellular energetics. Recently reported intercellular transport of mitochondria through tunneling nanotubes also play a role in the response to and treatments for ischemic injury. In this review we attempt to provide an overview of some of the molecular mechanisms and potential therapies involved in the alteration of cellular energetics with aging and injury with a neurobiological perspective.

1 Introduction

The world is experiencing considerable growth in its older population. Estimates from 2010 suggest that there were 524 million people aged 65 or older, this is expected to triple by 2050 (Suzman and Beard, 2011). Given these statistics, significant questions arise about productivity, health, well-being, independence, the need for social constructs to care for

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them, and factors that can positively impact the health of these individuals. The effect of stress or injury in old age is becoming an increasingly greater challenge. Declining mitochondrial function with aging plays a fundamental role in altered cellular energetics with aging and contributes greatly to outcome following injury (Biala *et al.*, 2015; Gomes *et al.*, 2013; Poulose and Raju, 2014). In this review, we aim to address this specific aspect by discussing the role of mitochondria in hypoxic/ischemic injury and the influence of aging on organ function.

2 The Mitochondrial Theory of Aging

In 1956, Harman suggested that free radicals result in cellular damage that accrues over time and causes aging (Harman, 1956). He later added to his theory in what has now become known as the mitochondrial theory of aging. He suggested that aging is due to accumulated free radical damage to mitochondria, impacting their ability to function (Harman, 1972). However there are mounting evidences that challenge the mitochondrial theory of aging (Lapointe and Hekimi, 2010). Results from rodent models with overexpression of genes important in redox regulation and models with ablation of these genes failed to support this theory. The accumulation of somatic mutations on mitochondrial DNA (mtDNA) has also been suggested to be through random genetic drift (Elson *et al.*, 2001). Further studies found that at least in short-lived animals, this model does not hold (Kowald and Kirkwood, 2013) and based on the relationship between transcription and mtDNA replication, the same authors recently reported that transcription could be the key to the selection advantage of mitochondrial deletion mutants in aging (Kowald and Kirkwood, 2014). Though theories built around mitochondria to address organismal aging remain controversial, the role of mitochondria in health, aging and disease is being increasingly recognized.

2.1 Structure and Function of Mitochondria

Mitochondria are a cellular organelle consisting of a simple outer phospholipid bilayer membrane, an intermembrane space, a complex inner phospholipid bilayer, and a mitochondrial matrix (Palade, 1953). The outer membrane contains VDACs, also known as mitochondrial porin proteins, which make it permeable to small molecules (Palade, 1953; Tomasello *et al.*, 2009). The intermembrane space is between the inner and outer membranes and play critical role in the transport of proteins across mitochondrial membranes, and oxidative phosphorylation (Gellerich, 1992; Herrmann and Riemer, 2010). The inner membrane is freely permeable to oxygen, carbon dioxide, and water (Alberts, 2008). It contains multiple folds called cristae, which significantly increase the total surface area of the inner membrane, allowing it to contain many proteins (Alberts, 2008; Palade, 1953) including transport proteins, all the electron transport chain complexes, and the ATP synthase complex (Alberts, 2008). The inner mitochondrial matrix contains the citric acid cycle reaction enzymes and substrates (Alberts, 2008).

Mitochondria produce energy and their numbers are particularly prominent in cardiac muscle, skeletal muscle, liver, kidney, and neuronal cells as these cells require significant energy for function. Mitochondria use the electron transport chain to produce usable chemical energy from electron donors like reduced nicotinamide adenine dinucleotide

(NADH) via a series of oxidation/reduction reactions where molecules transfer electrons and facilitate transmembrane proton transport resulting in an electrochemical gradient that drives adenosine triphosphate (ATP) synthesis (Mitchell, 1961).

Recent reports have suggested that mitochondria undergo rapid and constitutive metabolic oscillations in a coordinated manner in individual cells as well as in supracellular networks in the tissue (Porat-Shliom *et al.*, 2014). Reactive oxygen species (Aon *et al.*, 2004) and gap junctions (Porat-Shliom *et al.*, 2014) control the synchronization of mitochondrial activity, the oscillations were confirmed by intravital microscopy in living animals (Porat-Shliom *et al.*, 2014) These oscillations were found to disappear with interruption of circulation, inhibiting complex I, and by scavenging ROS. However, they persist but are not coordinated when carbenoxolone, a gap junction inhibitor, is administered.

2.2 Mitochondrial Complexes and the Electron Transport Chain

The electron transport chain consists of five enzyme complexes that are comprised of integral inner membrane proteins. They are NADH-CoQ reductase, Succinate-CoQ reductase, CoQ-cytochrome c reductase, cytochrome c oxidase, and ATP synthase (complexes I-V, respectively). Ubiquinone (CoQ) and cytochrome c are two freely diffusible molecules that mediate the transfer of electrons between complexes (Gao *et al.*, 2008). Oxygen is the final acceptor of electrons in this process.

2.2.1 Oxidative Stress—Oxidative stress arises when the system is unable to establish a balance between production and utilization of oxidant molecules. The excess production of ROS during oxidative stress has the potential to cause protein, DNA and lipid damage causing cellular injury, as observed in ischemia/reperfusion models (Bhat *et al.*, 2015; Walters *et al.*, 2016). Reactive oxygen species include hydrogen peroxide, hydroxyl radicals and superoxide anions. Nevertheless, it is known that cellular production of ROS is essential to the normal function of cells as they take part in specific signaling events (Finkel and Holbrook, 2000). ROS are produced inside the mitochondria as well as outside. The extra-mitochondrial sources of ROS include lipoxygenases, peroxisomes and NADPH oxidases. However, mitochondria are the major site of ROS production, inside the mitochondria, complexes I and III are the major sites. Though mitochondrial ROS has been attributed to one of the causes of aging, there are evidences to the contrary (Wang and Hekimi, 2015).

2.2.2 Mitochondrial Complex I—NADH enters the electron transport chain at complex I (NADH-CoQ reductase, or NADH dehydrogenase). NADH binds to the complex and is oxidized, donating 2 electrons. Electrons are transferred through- complex I flavin mononucleotide (FMN) prosthetic group and it is converted to $FMNH_2$ (Hirst, 2010). The electrons pass through a series of nine FeS clusters to Coenzyme Q (CoQ) (Murphy, 2009) and eventually to the primary electron acceptor, ubiquinone.(Sazanov and Hinchliffe, 2006) The fully reduced flavin in complex I also reduces O_2 to superoxide (Hirst, 2010). This also results in transfer of four protons from the matrix into the intermembrane space to support the proton motive force that drives ATP synthesis. Both forward and reverse electron flow generate superoxide radicals (Schonfeld *et al.*, 2010). Inhibition of complex I by rotenone increases superoxide production. The superoxide may be converted to hydrogen peroxide

(H_2O_2) by MnSOD within the mitochondria or react with NO to generate peroxynitrite (ONOO-).

2.2.3 Mitochondrial Complex II—Succinate-Q oxidoreductase (complex II) is the only enzyme that is part of both the citric acid cycle and the electron transport chain (Cecchini, 2003). In this reaction, succinate is oxidized to fumarate through a flavin adenine dinucleotide (FAD) cofactor and iron sulfur clusters mediate electron transfer to coenzyme Q. A heme group is also present but is believed to decrease reactive oxygen species production (Yankovskaya *et al.*, 2003). It does not contribute to the proton gradient by transporting protons.

2.2.4 Mitochondrial Complex III—Complex III has been known for a long time to be a significant site of ROS production in the ETC (Murphy, 2009). Q-cytochrome c reductase (complex III) is a dimer with each part containing protein subunits, iron sulfur clusters, and cytochromes (Iwata *et al.*, 1998). In a two step process called the Q cycle, ubiquinol is oxidized and two molecules of cytochrome c are reduced, also resulting in four protons being added to the intermembrane space (Trumpower, 1990). An intermediate in this cycle is a free radical called ubisemiquinone, which can leak electrons directly to oxygen, resulting in superoxide. Superoxide production is further enhanced when complex III is inhibited by antimycin A.

2.2.5 Mitochondrial Complex IV—Cytochrome c oxidase (Complex IV) consists of 13 subunits, two heme groups, and metal cofactors including magnesium, zinc, and three copper ions (Tsukihara *et al.*, 1996). It mediates the transfer of electrons to O_2, which is reduced to two H_2O molecules. Four reduced cytochrome c molecules serve as electron donors and four protons are consumed from the matrix to make H_2O. Four protons are also transferred from the matrix to the intermembrane space, increasing the electrochemical gradient and proton motive force. This complex is highly efficient and releases few partly reduced intermediates.

2.2.6 Mitochondrial Complex V—ATP synthase (complex V) is the final step of oxidative phosphorylation. It uses the proton motive force generated across the inner mitochondrial membrane to drive synthesis of ATP (Boyer, 1997). Three to four protons pass through the complex, driving molecular rotors named Fo and F1, and resulting in one unit of ATP (Fillingame and Steed, 2014; Jastroch *et al.*, 2010).

2.2.7 Oxidative Products and Effects (Complexes 1-III)—Mitochondrial electron transport generates superoxide as an inevitable by-product at complexes I-III (Turrens, 2003). So in the presence of oxygen, reactive oxygen species such as the superoxide radical (O_2^-) are generated in low levels. Over time, however, small amounts of free radical induced oxidative damage may accumulate, particularly during hypoxic or ischemic episodes (Chan, 2001). Glutathione peroxidase, catalase and superoxide dismutase are effective endogenous antioxidants that can help scavenge free radicals. In the absence of scavengers, ROS can cause deleterious effects on cellular functions. The transcription factors, Nrf-1 and Nrf-2 have been shown to control the expression of antioxidant response genes (Ohtsuji *et al.*, 2008). A decreased expression of several antioxidant response genes have been observed in

mice deficient in Nrf-2 (Itoh *et al.*, 1997). Environmental pollutants, therapeutics, and transient hypoxia have all been suggested and confirmed experimentally to be “hits” resulting in injury to mitochondria and specifically mitochondrial DNA (Nohl *et al.*, 1997). Mitochondrial DNA is especially susceptible to free radical induced damage as it is in close proximity to reactive oxygen species production and superoxide is unable to diffuse through the mitochondrial membranes (Gao *et al.*, 2008). Consequently, there is a major role for mitochondria in hypoxic-ischemic injury as well as age dependent decline in metabolic processes and organ function (Correia-Melo and Passos, 2015). Other neurodegenerative diseases such as Alzheimer’s disease (Aliev et al., 2002; Ng et al., 2014; Palacios et al., 2011) and Parkinson’s disease (Snow et al., 2010; Wu et al., 2011) have also shown key roles of age dependent decline of mitochondrial function and increased oxidative stress, although the focus of this review is on hypoxic-ischemic injury.

3 Hypoxic-Ischemic Injury

3.1 Definitions

Hypoxia refers to low levels of oxygen in the body or tissue. Hypoxemia, on the other hand, refers to low levels of oxygen in the blood. Ischemia occurs with a lack of blood flow to tissues. Ischemia always results in tissue hypoxia. However, hypoxia can occur without ischemia as in acute lung injury (decreased oxygen entering blood), anemia (decreased carrying of oxygen by blood), carbon monoxide poisoning (decreased delivery of carried oxygen to tissues), and other mechanisms. Ischemia can be global or focal. Global ischemia can be produced by traumatic hemorrhage, cardiac or pulmonary failure, sepsis and other mechanisms. Focal ischemia can be produced by embolic or thrombotic processes, injury, surgical clamping of a blood vessel, during organ transplantation, and other mechanisms. Whether by hypoxia or ischemia, or both, a dearth of mitochondrial oxygen impairs oxidative phosphorylation and mitochondrial function. As hypoxic and ischemic events are increased in elderly individuals, they are particularly prone to the resulting mitochondrial dysfunction.

3.2 Effect of Hypoxia/Ischemia

Hypoxic/Ischemic insults are important in the generation of reactive oxygen species (ROS). In unstressed healthy individuals, ROS are generated during cellular metabolism. Sources of ROS include xanthine oxidase, nicotinamide adenine dinucleotide reduction, and adenosine triphosphate production via the mitochondrial electron transport chain (Cairns *et al.*, 1997). Normally, cellular antioxidant systems effectively remove ROS. One mechanism by which this occurs is when superoxide dismutase reacts with superoxide radicals produced during cellular respiration to generate hydrogen peroxide, which is subsequently broken down by glutathione peroxidase and catalase (Winterbourn, 2013). However, during hypoxic/ischemic injury, ROS production by the mitochondria overwhelms antioxidant capacities, leading to cellular DNA damage, mitochondrial lipid peroxidation, disruption of Ca^{2+} homeostasis (Mattson *et al.*, 2000) (Murphy and Steenbergen, 2008), and mitochondrial membrane depolarization (Lemasters *et al.*, 2009). This results in cytochrome c release and cell death by apoptosis (Wu and Bratton, 2013). Thus, mitochondrial function is a crucial determinant of survival during ischemic injury (Brookes *et al.*, 2004).

3.3 Mitochondrial Trafficking

Intracellular trafficking of mitochondria is important in meeting local metabolic demand as well as in renewal and recycling of the organelle.(Chang and Reynolds, 2006). It has been suggested that motility of axonal mitochondria is important in plasticity and reliability of synaptic transmission (Sun *et al.*, 2013b). Intercellular transfer of mitochondria have been demonstrated in both in vitro and in vivo models and are reported to be facilitated by cellular portals formed by tunneling nanotubes (TNTs) (Gerdes *et al.*, 2007; Rogers and Bhattacharya, 2013). TNTs are cellular connections 100–800 nm in diameter and up to 100 μm long that contain a small cytoplasmic bridge and a surrounding phospholipid bilayer (Gerdes *et al.*, 2007). TNTs look like phyllopodia while forming and contain F-actin and motor proteins (Gerdes *et al.*, 2007; Rustom *et al.*, 2004). TNTs have been observed in various cell lines, including but not limited to adrenal cells (Bukoreshtliev *et al.*, 2009), kidney cells (Gurke *et al.*, 2008), and cardiac cells (Koyanagi *et al.*, 2005; Plotnikov *et al.*, 2008).

Unidirectional mitochondrial intercellular transfer within nanotubes has been demonstrated (Koyanagi *et al.*, 2005; Plotnikov *et al.*, 2008). Vibration and chemical inhibitors of TNT formation are noted to prevent or decrease mitochondrial intercellular transfer (Gurke *et al.*, 2008; Rustom *et al.*, 2004). Also, overexpression of the mitochondrial GTPase Miro1 has been shown to increase mitochondrial transfer and prevent lung injury by the mitochondrial poison rotenone, while knockdown leads to decreased transfer and loss of efficacy (Ahmad *et al.*, 2014). Among other stressors, oxidative stress leading to p53 activation has been shown to be a stimulant for TNT development in stressed cells to non-stressed cells based on the concentration difference in the S100A4 protein (Wang *et al.*, 2011c). Damaged neurons had decreased S100A4 and produced TNT, while cells with higher levels received the TNT. In another study, lung adenocarcinoma A549 cells without mitochondria due to treatment with ethidium bromide received mitochondria and recovered aerobic respiration from cells with functional mitochondria (Spees *et al.*, 2006). Not only do the cells recover respiration, they are also protected from endotoxin induced acute lung injury associated with the transfer of functioning mitochondria (Islam *et al.*, 2012). Another model using cigarette smoke also demonstrated that mitochondrial transfer from induced pluripotent cells decreased damage to lung epithelium (Li *et al.*, 2014). Given these results, using stem or progenitor cells as a vehicle for healthy mitochondrial transfer to cells with damaged mitochondria as a result of hypoxia or aging, and potentiating this transfer with Miro1 may provide significant therapeutic value but needs more investigation, especially with neuronal cells as few studies have been performed in these cell populations at this time (Las and Shirihai, 2014). Apart from acting as a connecting bridge between cells for mitochondrial transfer, TNTs may also serve important intercellular communication during cellular stress (Wang and Gerdes, 2015).

3.4 Nuclear-Mitochondrial Cross-talk

Mitochondrial structure and function are controlled by the 37 genes encoded in mtDNA as well as a large number of genes in nuclear DNA (Poulose and Raju, 2014). Among the 37 genes on the mtDNA, 13 code for proteins, 22 for tRNAs and 2 for ribosomal RNAs. The transcription and translation of the 13 genes coding for proteins on mtDNA involves a complex process participated by a number of proteins coded on the nuclear genome

(Hallberg and Larsson, 2014). Therefore the small number of genes on the mtDNA is not sufficient for the structure and function of mitochondria. The nuclear encoded proteins that are translated are translocated into the mitochondria by a well-orchestrated mechanism. Several molecular and genetic factors have broad impacts on the normal function of mitochondria as well as in the setting of age and ischemia. Therefore, nuclear-mitochondrial talk is an essential mechanism in mitochondrial homeostasis. In order to study nuclear-mitochondria cross talk, our laboratory developed a mitochondrial gene chip with probe sets representing the transcriptome of the genes on the mitochondria and that of the nucleus important for the structure and function of mitochondria, together called the mitoscriptome (Raju *et al.*, 2011). We found significant upregulation of genes involved in glycolytic pathways in cardiomyocytes subjected to hypoxia demonstrating a shift in energy production from mitochondria to glycolysis (Jian *et al.*, 2011b). Recently it has been found that humanin, a mitochondria derived peptide, exhibits strong cytoprotective actions against various stress and disease models and suggested to be part of a retrograde signaling that involves nuclear-mitochondria crosstalk (Gong *et al.*, 2014). This inter-organelle communication is important in the mitochondrial response to hypoxic-ischemic conditions, whether induced by stroke, myocardial-infarction or sepsis. About 1500 distinct proteins are estimated to be involved in the maintenance of mitochondrial structure and function (Calvo and Mootha, 2010), some of the master regulators that control physiological responses are well-studied.

3.3.1 Molecular Mediators of Mitochondrial Function in Hypoxic-Ischemic Injury—One of the hallmarks of hypoxia is the stabilization of HIF-1α and subsequent nuclear translocation with modulation of expression of a number genes important in energy metabolism (Ke and Costa, 2006; Salceda and Caro, 1997; Semenza, 2007). HIF-1 consists of two protein subunits: HIF-1β, which is constitutively expressed, and HIF-1α, which is continuously synthesized then degraded in a prolyl hydroxylase dependent manner (Solaini *et al.*, 2010) by the ubiquitin-proteasome system under normoxic conditions (Salceda and Caro, 1997). During low oxygen tension, proline hydroxylation does not occur and HIF-1α rapidly accumulates, binds with the β subunit and is translocated to the nucleus where it serves as a transcriptional activator of over 100 genes (Semenza, 2007). Many of these genes are involved in glycolytic pathways and lead to a switch in energy production from oxidative phosphorylation to glycolysis (Semenza, 1996). HIF-1 enhances glycolysis by upregulating synthesis. of glycolysis enzymes (Semenza, 1996), increasing glucose transporters, and blocking mitochondrial energy metabolism (Semenza, 2011). HIF-1 facilitates activation of pyruvate dehydrogenase kinase (PdK)1, which phosphorylates and inhibits pyruvate dehydrogenase (PDH), the rate limiting step leading to oxidative phosphorylation, from converting pyruvate to acetyl CoA to fuel the mitochondrial TCA cycle (Papandreou *et al.*, 2006) and blocks assembly of Fe/S clusters required for oxidative phosphorylation (Semenza, 2011). It also concomitantly blocks nuclear-mitochondrial crosstalk inhibiting the expression of mitochondrial encoded subunits in oxidative phosphorylation complexes (Gomes *et al.*, 2013). The Sinclair group (Gomes *et al.*, 2013) suggested the development of a pseudohypoxic state with progressive aging and a role for HIF-1, independent of PGC-1α, in modulating mitochondrial function. HIF-1 has an interesting interplay with a pleotropic transcription factor called c-MYC. c-MYC binding canonical sequence segments are found

on several genes related to mitochondrial biogenesis (Kim *et al.*, 2008; Li *et al.*, 2005) and overexpression of c-MYC was shown to prevent loss of mtDNA and cellular ATP levels with upstream inhibition (Gomes *et al.*, 2013). c-MYC appears to act via increasing transcription factor A mitochondrial (TFAM) and is critically important in hypoxia/ischemia. In a mitochondrial gene expression profiling of a rat model of hemorrhagic shock in our laboratory, c-MYC exhibited most change following the injury (Jian *et al.*, 2011b).

The c-MYC -HIF-1 interrelationship and their role in cellular homeostasis remain unsettled. Though there are contradicting results, HIF-1 modulation of c-MYC is evident from many studies. c-MYC increases both glycolysis and mitochondrial oxidative phosphorylation. Both c-MYC and HIF-1α are upregulated with hypoxia, yet HIF-1 directs c-MYC repression and inhibition of oxidative phosphorylation (Kim *et al.*, 2006), a result similar to Warburg reprogramming (Christofk *et al.*, 2008; Warburg, 1956). HIF-1 also impacts neovascularization, angiogenesis and cell survival. It has also been shown to be a critical determinant of lifespan in *C. elegans,* a nematode frequently used in aging research (Leiser and Kaeberlein, 2010). While Warburg postulated aerobic glycolysis in cancer, notwithstanding the anaerobic environment in the core of solid tumors, injury conditions such as ischemia or hemorrhage reflect an anaerobic status with mitochondrial functional deficiency and promotion of glycolysis. This is clearly evident in models like hemorrhagic shock where increased plasma lactate and decreased tissue ATP levels are consistently observed (Jian *et al.*, 2012; Pearce *et al.*, 1985). These relationships and others are depicted in Figure 1. Further investigations on the fine balance of function between HIF-1 and c-MYC in hypoxic/ischemic insult with the aging phenotype is likely to yield more information on the dysregulation of mitochondrial homeostasis.

One of the critical mediators of mitochondrial function is PGC-1α, the expression and activity of which have been demonstrated with several age-associated neurodegenerative diseases (Wenz, 2011). PGC-1α is a cofactor to peroxisome proliferator-activated receptor (PPAR) family transcription factors leading to increased mitochondrial fatty acid oxidation gene expression (Finck and Kelly, 2007). It also binds to and activates nuclear respiratory factor 1 (NRF1), a transcription factor that increases oxidative phosphorylation and also stimulates the synthesis of transcription factor A mitochondrial (TFAM), leading to mtDNA transcription, maintenance, and replication (Kang and Hamasaki, 2005). Additionally it targets and activates estrogen receptor related receptor (ERR) family proteins. ERRα increases nuclear respiratory factor 2 (NRF2), which regulates the cell cycle, cell differentiation, and mitochondrial biogenesis (Scarpulla, 2008). PGC-1α has also been noted to have effects on energy production and defense systems against ROS (Jian *et al.*, 2011b). PGC-1α activity is modulated by nutrient availability, calcium, ROS, insulin, thyroid hormone, estrogens, hypoxia, ATP demand, cytokines, and c-MYC (Puigserver and Spiegelman, 2003). It has also been noted to decrease with age (Anderson and Prolla, 2009). A SIRT1 pathway that regulates mitochondria independently of PGC-1α was recently postulated (Gomes *et al.*, 2013). These researchers were able to revert key biochemical parameters in 22-month old mice to that of 6-month old mice by treating these mice with NAD+, a substrate and therefore a modulator of SIRT1 activity, indicating that regulation of mitochondrial function can alter aging trajectory.

3.4.1 Age Related Effect of Hypoxia/Ischemia on Cells and Mitochondria— Aging, as discussed by Harman, leads to mitochondrial dysfunction (Harman, 1972). Mitochondrial dysfunction causes energy failure and is associated with multi-organ dysfunction in severely injured patients (Cairns *et al.*, 1997). Consequently, mitochondria are a common denominator in the increased mortality, injury, and organ dysfunction associated with aging during hypoxia and ischemia. Mitochondria are increasingly implicated as central players in the development of ischemic cell death both through impairment in generating ATP for cell function and as key mediators in cell death pathways (Sims and Muyderman, 2010). This has been attributed to multiple mechanisms.

During hypoxia or ischemia, oxidative phosphorylation via the electron transport chain is inhibited or reduced, resulting in accumulation of superoxide radicals along with decreased ATP (Solaini *et al.*, 2010). Superoxide at low levels does little cellular damage by itself; however, at higher levels, pathologic free radicals such as hydro-peroxyl radicals, hydroxyl radicals, and peroxynitrite (Stowe and Camara, 2009) result in oxidative stress that can damage DNA, lipids, and proteins, (Wheaton and Chandel, 2011). This oxidative stress, in conjunction with calcium increases due to glutamate toxicity (in the brain) and/or ischemia induced loss of efflux associated with less Na^+/K^+ ATPase and Na^+/Ca^{+2+} exchanger activity, causes the inner mitochondrial membrane to become more permeable with resultant loss of the mitochondrial membrane potential (Green and Kroemer, 2004). This leads to mitochondrial swelling with release of cytochrome *c* and apoptotic protease activating factors (Murphy *et al.*, 1999) into the cytoplasm. Together, they activate caspases and induce apoptosis (Zou *et al.*, 1997). This process is amplified when aged cells are exposed to injury, particularly hypoxic/ischemic injury as progressive loss of mitochondrial function potentiates further injury. Less efficient mitochondria in aged cells have increased free radical generation and decreased energy production during stress (Nohl *et al.*, 1997; Sasaki *et al.*, 2008b). Consequently, not only is the damage greater in aged cells for a given degree of injury, the healing response is also diminished (Gupta *et al.*, 2004). There are also age-related decreases in the activities of mitochondrial carrier proteins—such as for phosphate, ATP/ADP (Paradies and Ruggiero, 1991; Tummino and Gafni, 1991) and Ca 2+ (Hansford and Castro, 1982), adenine nucleotide (Kim *et al.*, 1988; Nohl and Kramer, 1980; Tummino and Gafni, 1991), and pyruvate (Paradies and Ruggiero, 1990). Humanin, a mitochondria-derived small peptide has been shown to exhibit strong cytoprotective actions against pathological stress (Lee *et al.*, 2013a). Interestingly this 24-amino acid peptide is derived from a 75bp open reading frame in the 16S ribosomal RNA sequence on the mtDNA. One recent study found that a humanin-derivative, AGA(C8R)-HNG17, enhanced the activity of ATP synthase complex (Cohen *et al.*, 2015). Humanin is also implicated to play a role in lifespan extension (Gong *et al.*, 2014). As such mitochondria are believed to be a key modulator of neuronal viability during hypoxic/ischemic stress.

3.4.2 Mitochondrial dynamics and role in cell death—Hypoxic-ischemic insults are associated with increased apoptosis (programmed cell death). Mitochondrial control of apoptosis has been extensively studied and a number of players included in this mechanism are known. During ischemia, increased levels of ROS and influx of calcium leads to membrane permeability transition, and release of cytochrome c from mitochondrial

intermembrane space leading to the activation of the apoptosome and caspase mediated apoptosis (Mattson *et al.*, 2000) (Bonanni *et al.*, 2006). Studies showed an increased release of cytochrome c with aging (Marzetti *et al.*, 2013). Calcium mediated activation of mitochondrial calpains 1 and 10 results in the cleavage of AIF from inner membrane and translocation to nucleus facilitating caspase independent programmed cell death (Polster, 2013). A growing number of known proteins are known to be involved in initiating and executing mitochondria-mediated apoptosis or inhibiting the process, and these include Bax, Bad, Bid, Apaf-1, Bcl-2, and Bcl-xL.

Cellular machinery is a robust biological system with meticulous built-in mechanisms to maintain homeostasis. Autophagy is one such mechanism that works together with the ubiquitin-proteosome system to recycle damaged organelles and act as a survival mechanism in nutrient poor conditions. Activation of autophagy has been observed following cerebral ischemia (Polster, 2013) and declining autophagy is noted with age (Wang *et al.*, 2011a). Inhibition of mTOR by rapamycin was found to augment autophagy and consistent with this observation, rapamycin prolonged longevity in mice (Ehninger *et al.*, 2014; Harrison *et al.*, 2009). These results demonstrate a key role for autophagy in the restoration of cellular homeostasis and aging phenotype. An autophagy process called mitophagy is utilized by cells to clear damaged mitochondria. This is a critical process for healthy mitochondrial biogenesis considering the dynamic nature of this organelle, which undergoes constant fission and fusion process. Mitophagy involves a selective recruitment of mitochondria into isolation membranes and fusion with lysosomes resulting in the elimination of entrapped mitochondria (Kane and Youle, 2010). However, it is not clear how soon this process is effected in the case of sudden injuries such as myocardial infarction, stroke or hemorrhagic shock. Nevertheless, it is known that one hour after induction of stress by mitochondrial uncouplers, Parkin can translocate from cytosol to mitochondria (Kane and Youle, 2010). PINK1 is required for the Parkin recruitment to mitochondria (Sebastian *et al.*, 2012). In healthy cells, PINK1 is rapidly degraded by proteolysis and maintains low levels, where as PINK1 hydrolysis is inhibited in damaged mitochondria. Parkin inhibits mitochondrial fusion by ubiquitinylating mitofusins (Gomes *et al.*, 2011). Dynamin-related protein 1 (Drp1) and Fission 1 (Fis1) are fission-promoting proteins, whereas Mitofusin 1 and -2 are mainly responsible for outer membrane fusion, and Opa1 mediates inner membrane fusion. Mitofusin 2 is also reported to tether endoplasmic reticulum to mitochondria (Ding and Yin, 2012). It has been shown that starvation resulted in elongated mitochondria, resulting in resistance to autophagic degradation. This is postulated to be due to increased cAMP and activation of protein kinase A resulting in phosphorylation of Drp1 (Gomes *et al.*, 2011; Rambold *et al.*, 2011). It may be noted that a major pathway implicated in caloric restriction mediated longevity is increase in the expression and/or activity of SIRT1, and SIRT1 is known to promote mitochondrial biogenesis. In lower organisms it has been shown that, though controversial, resveratrol can mimic the beneficial effects of caloric restriction. In addition, Bnip3 and Nix are highly induced during hypoxia and are important in mitochondrial autophagy. Mitochondrial fission and fusion control quality of the mitochondria, and together with mitophagy prevent accumulation of damaged mitochondria and maintain mitochondrial homeostasis.

3.5 Age Related Effects of Hypoxia/Ischemia on Organ Function

3.5.1 Neurologic—The CNS is highly susceptible to mitochondrial impairment because of its aerobic requirements. It is reported that blood flow to an average brain is 15% of the cardiac output (Udomphorn *et al.*, 2008). While the human brain comprises only 5% of the body, it is responsible for 20% of respiration and is dependent on glucose and oxygen for energy. More injury occurs with smaller insults compared to other tissues (Wang and Michaelis, 2010). It has been shown that young individuals have increased neuronal aerobic glycolysis compared to aged individuals (Goyal *et al.*, 2014). Aerobic glycolysis, also known as Warburg reprogramming and first described in cancer cells, is defined as glucose utilization in excess of that used for mitochondrial respiration despite sufficient oxygen to completely oxidize glucose. Positron emission tomographgy based studies suggest that aerobic glycolysis commonly occurs in healthy adult brains (Fox and Raichle, 1986; Fox *et al.*, 1988; Vaishnavi *et al.*, 2010). Changes in brain energetics, neuronal phosphate, and ATP metabolism occur with age (Forester *et al.*, 2010), and elderly individuals have virtually absent global neuronal aerobic glycolysis (Goyal *et al.*, 2014), which creates a pseudohypoxic state. This is particularly relevant in the face of hypoxic injury, as aged individuals have less oxygen dependent cellular metabolism needed for post injury repair.

The unique structure of the neuron necessitates mitochondrial transport to facilitate local energy demand. Mitochondria are trasported to synaptic terminals along microtubules to meet the energy demand due to synaptic transmission (Ma *et al.*, 2009). About 20–30% of axonal mitochondria are reported to be motile in mature neurons (Lin and Sheng, 2015), though the localized non-motile mitochondria serve local energy needs the motile ones may have complementary functions in energy needs. Furthermore it has been suggested that there is a correlation between mitochondrial membrane potential and the direction of mitochondrial transport (Miller and Sheetz, 2004). The speed of mobilization is important in critical events and influence of age and hypoxic/ischemic injury in mitochondrial trafficking may be an important factor in determining neuronal survival following injury.

Stroke is a major cause of death in the United States, with one person dying from stroke every four minutes (Mozaffarian *et al.*, 2015). The incidence of stroke onset seems to be higher in men at middle age than older age, whereas women show fewer stroke incidences during middle age that increases significantly at older age. Several preclinical studies show that estrogen treatment is beneficial after stroke, but its effects have been found to be age and sex dependent and in particular estrogen therapy might be detrimental in aged women (Kim and Vemuganti, 2015).

Stroke may be associated with local or global ischemia depending on the nature of the initiating event. For example, embolic occlusion of the middle cerebral artery can result in focal ischemia while heart failure can cause a low flow state resulting in global ischemia. During stroke, in the penumbral region, large decreases are seen in ATP (Folbergrova *et al.*, 1995). Some of the ADP generated from ATP hydrolysis is further metabolised to AMP and ATP. The AMP in ischemic tissue is then converted to inosine and hypoxanthine resulting in overall depletion of the adenine nucleotide pool (Onodera *et al.*, 1986). Ischemic

preconditioning has been suggested to modulate miRNAs that are upstream of neuroprotective signaling (Vemuganti, 2010).

Another frequent cause of neuronal injury is traumatic brain injury (TBI). Adults aged 75 and older have the highest rates of traumatic brain injury related hospitalization and death (Thompson *et al.*, 2006). Repeated stress prior to TBI increase expression of cerebral mitochondrial electron transport chain complex proteins (Xing *et al.*, 2013). Traumatic brain injury frequently results in intracranial hemorrhage leading to increased intracranial pressure and reduced cerebral perfusion pressure, which causes ischemia. According to a Congressional Research Service report of 2014, over 300,000 Defense service personnel of the United States suffered traumatic brain injury during the period 2000–2014 which include wars in Iraq and Afghanistan (Fischer, 2014). Neurologic outcomes are worse for individuals at the extremes of age following ischemia. In one experiment, juvenile, young adult, middle-aged, and aged (18–19 months) mice had transient middle cerebral artery occlusion. On postoperative day seven, aged mice had significantly increased infarct volume. In addition, aged mice had prolonged disability and less functional recovery after stroke. The aged animals had decreased mitochondrial function and less antioxidant detoxification following ischemia, thereby inducing oxidative damage (Li *et al.*, 2011b). While the study by Li and coworkers implied the neurological deficits were associated with increased infarct volumes sustained with age, another study found that tissue loss failed to explain the increased functional deficits seen in aged animals and suggested that prolonged edema, increased opening of the blood-brain barrier and increased neurodegeneration were responsible for age-related differences in outcome (Onyszchuk *et al.*, 2008). Some groups have suggested that altered apoptotic proteins with age play a role. There is age related increased expression of apoptosis proteins (heat shock protein 27, hippocalcin, and LANP [acidic nuclear phosphoprotein]) after injury (Sun *et al.*, 2013a). Less cellular proliferation and differentiation into neurons after injury in aged animals has been noted (Sun *et al.*, 2005). Electrolyte and neurotransmitter excess may also contribute to age related neurotoxicity. Higher levels of K^+ and glutamate with aging disrupt ionic and neurotransmitter homeostasis in neuronal cells through injury induced activation of AMPA (non NMDA) and NMDA receptors leading to calcium influx (Yi and Hazell, 2006) and apoptosis. This glutamate mediated excitotoxicity is known to cause expansion of the injury; however, glutamate receptor antagonists have been ineffective (Yi and Hazell, 2006). Others have suggested metabolic differences contribute, noting that brain pH and high energy phosphate levels remain lower for longer in older gerbil brains during transient ischemia (Funahashi *et al.*, 1994). The authors suggested that brain mitochondria from older animals are less capable of responding to oxidative stress brought on by ischemia and that oxidative damage accumulates as the pH stays lower. Increased oxidative damage due to amplified levels of free radicals with age is another mechanism by which neurologic outcomes are worse after cerebral ischemia (Buga *et al.*, 2008; Itoh *et al.*, 2013). Superoxide levels are greater in the brains of aged mammals and birds during oxidative stress (Sasaki *et al.*, 2008b). This is likely due to not only increased superoxide generation (Sasaki *et al.*, 2008b), but also reduced antioxidant levels following ischemic stroke (Flamm *et al.*, 1978). Importantly, a recent study identified that cardiolipin oxidation generates mitochondrial death signals and the global lipodomics-based study in an experimental traumatic brain injury model

demonstrated significant oxidation of polyunsaturated cardiolipin following the injury (Ji *et al.*, 2012).

The changes to neuronal mitochondria during ischemic stress in aged individuals have been studied by multiple groups. A study of age related changes in the blood brain barrier revealed altered function that was associated with a decrease in the number of mitochondria in endothelial cells of brain capillaries in monkeys (Mooradian, 1988). Not only are there less mitochondria, but the remaining neuronal mitochondria have associated functional decline (Xu *et al.*, 2008). The etiology of the functional decline is likely multifactorial. The age related mutations of mitochondrial DNA lead to less effective production of various proteins needed for respiratory chain function (Bowling *et al.*, 1993). Over time various studies have reported a decline in mitochondrial function in aged rats associated with impairment of complexes in the respiratory chain (Davis *et al.*, 1997; Tatarkova *et al.*, 2011).

3.5.2 Cardiac—Aging increases propensity for cardiac ischemia injury. Aged individuals have demonstrated higher mortality after myocardial infarction despite similar infarct size to younger patients (Corsini *et al.*, 2006; Day *et al.*, 1987). It has been reported that ROS generated from mitochondria is significantly elevated in the heart with progression of age (Judge *et al.*, 2005). One study examined the cardiac effects of ischemia in aged versus adult rat hearts and found that age results in greater tissue damage (creatine kinase measurements 3.4 times greater) and limits hemodynamic recovery (pressure 31% vs 57% of preischemic baseline) (Lesnefsky *et al.*, 1994). Consequently, aged hearts are more susceptible than the adult hearts to ischemia-reperfusion injury. There are likely multiple mechanisms by which this occurs; ionotropic, metabolic, genetic, oxidative stress, and hormonal pathways have all been suggested. Many of these mechanisms involve the mitochondria.

A component of the increased cardiac injury seen with aging may be ionic imbalance (Tani *et al.*, 1997). Aged individuals start with higher intracellular sodium levels and have greater sodium increase with injury associated with a decline in myocardial function. The lack of cellular ATP due to hypoxia and mitochondrial dysfunction with aging may limit the function of the sodium-potassium ATPase, resulting in higher intracellular sodium levels.

Changes in metabolism due to altered mitochondrial gene expression in aged individuals following hypoxia/ischemia may also explain the increased cardiac injury. A number of genes related to cellular energetics are altered with age following trauma-hemorrhage based on an analysis with a custom-made rodent mitochondrial gene chip (RoMitochip) in 6 and 22 month old rats (Jian *et al.*, 2011b). Aged rats had a decline in the number and amplitude of expression of mitochondria-related genes compared to the younger rats following trauma-hemorrhage.

Aged animals appear to have less ability to withstand significant oxidative stress and have more oxidative injury following cardiac ischemia. One study found that aging selectively decreases the oxidative capacity of rat heart interfibrillar mitochondria. They found increased oxidative damage occurs in aged hearts, noted via increased oxidation of cardiolipin in the inner mitochondrial membrane following ischemia (Lesnefsky *et al.*, 2009).

Hormonal changes may also account for the increased cardiac injury with aging seen following hypoxic/ischemic injury. Based on proteomic screens of mitochondria, there appears to be a highly selective response to estradiol (E2) deficiency in aged versus adult rat hearts (Korzick and Lancaster, 2013) after ischemic injury. They suggested that estradiol deficiency induced perturbations of electron transport chain (ETC) proteins may upset the stoichiometry of the ETC and contribute to increased ROS production and cardiac injury with aging.

There is an association between higher levels of mitochondrial DNA damage and coronary atherosclerotic heart disease (Ballinger, 2005; Corral-Debrinski *et al.*, 1992). Corral and coworkers specifically noted that in subjects with coronary artery disease certain mitochondrial DNA deletions were increased 7,220-fold over age-matched controls (Corral-Debrinski *et al.*, 1992). So not only are there increased errors in mitochondrial DNA, there are also decreased absolute amounts. In a model of coronary artery disease where the left anterior descending artery was ligated for 4 weeks, the mitochondrial DNA copy number was noted to decrease significantly. Interestingly, associated decreased complex I, complex III, and complex IV levels and activities were also observed (Ide *et al.*, 2001). Therefore, worse outcomes in aged individuals with cardiac ischemia are associated with mitochondrial DNA damage leading to decreased mitochondrial function. Consequently, modulation of mitochondrial respiration and function during and immediately following an episode of ischemia can attenuate the extent of myocardial injury (Chen *et al.*, 2007) and may maintain cardiac function in the context of injury and aging (Judge and Leeuwenburgh, 2007).

3.5.3 Interconnectedness of Mitochondria in Different Tissues, Mitokines— Interestingly, a recent study showed that mitochondrial perturbations in one tissue may trigger mitochondrial stress response in distal tissues (Durieux *et al.*, 2011). This provides a mechanism by which multiorgan dysfunction and survival can be affected in aged individuals exposed to ischemic insults in one tissue. Retrograde signaling by mitochondrial unfolded protein response (UPR) to the nucleus is suggested to be a likely mechanism of mitochondrial control of metabolic events following stress. Extension of such signaling events through hypothesized “mitokine” messengers to the distal parts of the body needs further investigation to substantiate (Riera and Dillin, 2015). One study that may support this hypothesis is the demonstration that neuronal ROS signaling through SKN/NRF2 may be sufficient to extend lifespan extension in *C. elegans* (Schmeisser *et al.*, 2013). If such a scenario exists, as a result of multi-tissue extension of mitochondria dysfunction, increased age significantly increases predisposition to critical illness, complications, and poor healing and is a strong independent risk factor for mortality after focal ischemia.

3.5.4. Age Related Effects of Global Hypoxia/Ischemia on Survival—While focal ischemia as described frequently has organ specific effects, global ischemia can cause multiple organ system failure. Traumatic hemorrhage is one of the models used to investigate the effects of global hypoxia and ischemia. In fact, almost half of deaths due to trauma are due to hemorrhage or its resultant hypoxic/ischemic injury (Curry *et al.*, 2011). Following hemorrhagic shock, aging has been shown to increase tissue damage (Mees *et al.*, 2008) and particularly amplified the effects of hypoxia/ischemia after trauma (Gong *et al.*,

2004; Gong *et al.*, 2005; Thompson *et al.*, 2006). Shock index (heart rate/systolic blood pressure) has been found to be an indicator of mortality in trauma patients (King *et al.*, 1996) and age multiplied by shock index is an even better predictor of early mortality in elderly patients (Zarzaur *et al.*, 2008). Consequently, increased age is associated with worse prognosis in these scenarios.

4 Pharmacologic Therapies

While time dependent thrombolytic agents like tissue plasminogen activator (tPA) exist to restore blood flow, few treatments improve outcomes once ischemic injury has occurred or after the three hour time window, especially in aged individuals. Several agents that are shown to have profound effect on mitochondrial function and have therapeutic potential for hypoxic/ischemic injury are being investigated in multiple laboratories.

4.1 Agents with Multiple Mechanisms

4.1.1 Sirtuins and Resveratrol

4.1.1.1 Overview: In response to acute injury conditions, cellular machinery can rapidly mobilize molecular pathways through posttranslational modifications, rather than relying solely on transcriptional control. Therefore processes such as phosphorylation-dephosphorylation and acetylation-deacetylation become important in restoration of cellular homeostasis underlining the significance of regulatory mediators like sirtuins, AMPK and PGC-1 in the control of mitochondrial function. Sirtuins are a class of NAD^+ dependent histone deacetylases (Imai *et al.*, 2000; Landry *et al.*, 2000; Smith *et al.*, 2000) that may also have mono-ADP ribosyl transferase (Frye, 1999; Haigis *et al.*, 2006), demalonylation (Du *et al.*, 2011), and desuccinylation activities (Du *et al.*, 2011). They were first discovered in yeast as a transcriptional repressor called silent information regulator 2 protein (Sir2) (Klar *et al.*, 1979; Rine and Herskowitz, 1987). All eukaryotes encode sirtuins in their genomes as sirtuins have important functions in regulating cellular stress responses (Brunet *et al.*, 2004; Dai *et al.*, 2014; Maksin-Matveev *et al.*, 2015), mitochondrial biogenesis (Brenmoehl and Hoeflich, 2013), apoptosis (Alcendor *et al.*, 2004; Motta *et al.*, 2004), metabolism (Purushotham *et al.*, 2009), fatty acid oxidation (Hirschey *et al.*, 2010), and inflammation (Cao *et al.*, 2013; Liu and McCall, 2013).

4.1.1.2 Types of Mammalian Sirtuins: Mammals have seven sirtuins (SIRT 1–7) distributed in different subcellular compartments. SIRT 1 and 2 are located in the nucleus and cytoplasm, SIRT 3, 4, and 5 are located in the mitochondria, and SIRT 6 and 7 are located in the nucleus (Haigis and Guarente, 2006; Michishita *et al.*, 2005). SIRT 1–3 primarily function by deacetylation, and deacetylation of histones leads to DNA coiling and gene silencing (Braunstein *et al.*, 1993). SIRT 4–7 have weaker deacetylase activity (Du *et al.*, 2011; Haigis *et al.*, 2006; Michishita *et al.*, 2008). SIRT 4 has ADP ribosyl transferase activity (Haigis *et al.*, 2006), and SIRT 5 also has demalonylation and desuccinylation activity (Du *et al.*, 2011). SIRT1 is the most well studied among all sirtuins.

4.1.1.3 Regulators and Targets: SIRT1 is the mammalian ortholog of yeast Sir2 and has numerous regulators and targets. SIRT1 expression and activity have been shown to increase

after exercise (Ferrara *et al.*, 2008) and with ischemic preconditioning (Hsu *et al.*, 2010). SIRT1's activity is NAD^+ dependent (Imai *et al.*, 2000). Nicotinamide phosphoribosyltransferase (Nampt) catalyzes the production of nicotinamide mononucleotide (NMN) and is the rate limiting enzyme in NAD^+ production (Imai, 2011). Nampt levels are reduced with aging and stress (Hsu *et al.*, 2009), resulting in decreased NAD^+ and decreased SIRT1 activity (Imai, 2011). Accordingly, overexpression of Nampt in the heart (Hsu *et al.*, 2009) and brain (Erfani *et al.*, 2015) has been shown to reduce infarct size and apoptosis in response to ischemia and reperfusion. In a negative feedback loop, Nampt is also regulated by SIRT1 mediated deacetylation and inactivation of its transcription factors (Ramsey *et al.*, 2009).

Many other regulators have also been shown to influence SIRT1 activity. Hu antigen R (HuR) is one that dissociates from SIRT1 mRNA during oxidative stress thereby destabilizing it (Abdelmohsen *et al.*, 2007). Other regulators include but are not limited to C-Jun N-terminal kinase 1 (JNK1) (Nasrin *et al.*, 2009), cyclin B/cyclin-dependent kinase 1 (Cdk1) (Sasaki *et al.*, 2008a), small ubiquitin-related modifier 1 (SUMO1)/sentrin specific peptidase 1 (SENP1) (Yang *et al.*, 2007), caspases (Ohsawa and Miura, 2006), MicroRNAs, (miR-34a (Yamakuchi *et al.*, 2008), miR-134 (Gao *et al.*, 2010), miR-199a (Rane *et al.*, 2009), and miR-217 (Menghini *et al.*, 2009)), insulin-like growth factor 1 (Vinciguerra *et al.*, 2010), hypermethylated in cancer (repressor) (Chen *et al.*, 2005b) and deleted in breast cancer 1 (repressor) (Zhao *et al.*, 2008)

Histones are a significant target of SIRT1. When activated, SIRT1 deacetylates histones, such as the lysine 26 residue of histone 1 (H1K26), lysine 9 residue of histone 3 (H3K9), and lysine 16 residue of histone 4 (H4K16). This results in tight DNA coiling and transcriptional silencing (Vaquero *et al.*, 2004; Vaquero *et al.*, 2007). SIRT1 is known to have two nuclear localization signals and two nuclear export signals have been noted (Tanno *et al.*, 2007). During ischemic stress, SIRT 1 is shuttled out of the nucleus and into the cytoplasm leading to decreased deacetylation and decreased SIRT1 function in aged hearts compared to young hearts (Tong *et al.*, 2013). Preferentially overexpressing nuclear SIRT1 has been shown to suppress apoptosis in cells exposed to oxidative stress (Tanno *et al.*, 2007). SIRT1 also has multiple non-histone targets. It binds to and deacetylates hypoxia inducible factor 1α (HIF-1 α) at Lys674, which inactivates it leading to repression of HIF-1 target genes (Lim *et al.*, 2010). SIRT1 also catalyzes PGC-1α deacetylation which impacts cellular metabolism and mitochondrial biogenesis (Nemoto *et al.*, 2005). PGC-1α and SIRT1 appear to be part of a pathway also involving adenosine monophosphate activated protein kinase (AMPK), a master switch sensing and regulating cellular energy processes (Canto *et al.*, 2009). AMPK activation increases NAD^+ levels, leading to SIRT1 activation and deacetylation of targets such as PCG-1α and forkhead box proteins (FOXO1 and FOXO3a) (Canto *et al.*, 2009), transcription factors for genes that modulate metabolism, upregulate manganese superoxide dismutase, and apoptosis (Hsu *et al.*, 2010). SIRT1 also stimulates AMPK by deacetylating serine/threonine kinase 11 (LKB1), an upstream kinase of AMPK (Wang *et al.*, 2011b). SIRT1 represses genes controlled by the beta oxidation regulator peroxisome proliferator-activated receptor-gamma (PPAR-γ) by docking with its cofactors nuclear receptor co-repressor and silencing mediator of retinoid and thyroid

hormone receptors leading to attenuated adipogenesis, lipolysis, and increased lifespan (Picard *et al.*, 2004).

SIRT1 inactivates p53 by deacetylating the C-terminal Lys382 residue and inhibits stress induced p53 transcription (Cheng *et al.*, 2003; Vaziri *et al.*, 2001). Active Regulator of SIRT1 (AROS) facilitates this process (Kim *et al.*, 2007b). This leads to increased anti-apoptotic molecules like thioredoxin-1 and Bcl-xL, and decreased pro-apoptotic molecules like Bax and cleaved caspase-3 (Hsu *et al.*, 2010). Additionally, the cell-cycle and apoptosis regulator E2F1 induces SIRT1 expression while SIRT1 inhibits E2F1 activity (Wang *et al.*, 2006).

SIRT1 has a complex feedback loop with the inflammatory cytokine NF-κB. SIRT1 directly inhibits NF-κB signaling via deacetylating its p65 subunit and indirectly by increasing NF-κB inhibitors such as AMPK, PPARα and PGC-1α (Kauppinen *et al.*, 2013). NF-κB diminishes SIRT1 activity through miR-34a, IFN-γ, and ROS (Kauppinen *et al.*, 2013). Nitric oxide, another molecule implicated in inflammatory processes, also diminishes SIRT1 activity by nitrosylation (Shinozaki *et al.*, 2014).

4.1.1.4 Sirtuin Activators – Resveratrol: One of the most studied sirtuin activators is resveratrol. Resveratrol is a naturally occurring polyphenol compound synthesized in many plants, such as peanuts, blueberries, pine nuts, and grapes, which protects them against fungal infection and ultraviolet irradiation (Bavaresco, 2003). It is a significant component of red wine and has been suggested to explain the “French paradox” in which the southwestern population of France has a low occurrence of coronary heart diseases and cardiovascular diseases despite a high saturated fat diet (Renaud and de Lorgeril, 1992). It has anti-cancer (Udenigwe *et al.*, 2008), anti-inflammatory (Chen *et al.*, 2005a; Udenigwe *et al.*, 2008), antiapoptotic (Baarine *et al.*, 2011; Nicolini *et al.*, 2001), antioxidant (Chang *et al.*, 2012; Spanier *et al.*, 2009), antidiabetic (Chang *et al.*, 2012), and antiviral (Clouser *et al.*, 2012) properties. It is a potent activator of SIRT1 by lowering SIRT1’s Michaelis constant for its acetylated substrate and NAD^+ (Howitz *et al.*, 2003). Consequently, it is often used to increase sirtuin activity as well as expression in in vitro as well as in vivo models. While this effect is strongly supported (Alcain and Villalba, 2009; Pervaiz, 2003; Raval *et al.*, 2008; Sun *et al.*, 2010), the underlying mechanisms are not fully understood (Zhang *et al.*, 2011). Recently it has been suggested that the effect of resveratrol on SIRT1 is a secondary effect of its cognate inhibitory interaction with phosphodiesterase (PDE) (Chung *et al.*, 2012; Park *et al.*, 2012) as shown in Figure 2. The investigators demonstrated a rolipram mimicking effect for resveratrol, resulting in increased cAMP, activation of AMPK and augmented levels of NAD+. AMPK phosphorylates the mitochondrial biogenesis factor PGC-1α and augmented NAD+ levels lead to enhanced SIRT1 activity and deacetylation of PGC-1α. Phosphorylation and deacetylation are the necessary and sufficient condition for the activation of PGC-1α. However later studies by Sinclair and colleagues demonstrated a dose dependent target specificity for resveratrol, with SIRT1 being the primary target at low concentrations and PDE at higher concentrations (Price *et al.*, 2012). Further studies are necessary to determine whether additional targets exists for resveratrol and the contribution of SIRT1 activation in in vivo studies using resveratrol. A recent study published from our

laboratory demonstrates that salutary effect of resveratrol in prolonging life after severe hemorrhage could be at least partially mimicked by the STAC SRT1720 (Ayub *et al.*, 2015).

In one study it was found that oral administration of resveratrol is associated with 70% absorption, but a bioavailability of 1% (Walle, 2011). It has a half-life of approximately 9 h and its phenol groups are rapidly conjugated in the liver with sulfate and glucuronic acid (Walle *et al.*, 2004). Its metabolites remain in the plasma significantly longer (Pervaiz and Holme, 2009). It is distributed to the liver, kidney, heart, and brain, among others (Andres-Lacueva *et al.*, 2012; Clark *et al.*, 2012; Walle, 2011). Greater than 50% of resveratrol and its metabolites are protein bound in plasma (Burkon and Somoza, 2008; Jannin *et al.*, 2004). It is predominately eliminated by the kidneys (Boocock *et al.*, 2007). In summary, resveratrol is frequently used experimentally to increase sirtuin activity and also has pleotropic downstream effects. Many other SIRT1-activating compounds (STACs) have been synthesized and analyzed (Lavu *et al.*, 2008). Many appear to stimulate SIRT1's enzymatic activity allosterically (Dai *et al.*, 2010). Clinical trials on diabetes, aging, obesity, cardiovascular disease and neurologic disease are in progress to evaluate the efficacies of resveratrol formulations and STACs such as SRT501, SRT2104, and SRT2379 (Camins *et al.*, 2010).

4.1.1.5 Role of SIRT1 and Resveratrol in Hypoxia, Ischemia, and Reperfusion: Sirtuins play a key role in the cellular response to injury by influencing metabolic pathways, cell death, and repair (Poulose and Raju, 2015). After the publication of mechanistic studies linking SIRT1 and resveratrol to longevity, a large number of laboratories began investigating them in a number of models in health and disease, both in vitro and in vivo. However human and non-human primate studies have lagged behind. SIRT1 and AMPK, irrespective of whether direct or indirect target of resveratrol, are stress dependent metabolic sensors that respectively deacetylate and phosphorylate PGC-1α to affect mitochondrial function and biogenesis (Canto and Auwerx, 2009). After ischemia and reperfusion, studies have noted a reduction in SIRT1 mRNA and protein expression (Hsu *et al.*, 2010). The effect on and modulation of SIRT1 levels with ischemia/reperfusion has been studied in multiple tissues.

4.1.1.5.1 Neurologic: SIRT1's neuroprotective effects have been demonstrated in multiple studies of ischemic stroke, traumatic brain injury, and other neurodegenerative diseases. A direct role for SIRT1 in ischemic stroke is suggested by the fact that SIRT1 knockout mice have increased infarct size when subjected to middle cerebral artery occlusion (Hernandez-Jimenez *et al.*, 2013; Liu *et al.*, 2013a). SIRT1 activators decrease infarct size (Gao *et al.*, 2006; Huang *et al.*, 2001; Li *et al.*, 2012; Lu *et al.*, 2006; Tsai *et al.*, 2007; Yousuf *et al.*, 2009) while SIRT1 inhibitors had an adverse effect (Hernandez-Jimenez *et al.*, 2013). Administration of the SIRT1 activator resveratrol remarkably enhances glucose and ATP levels and decreases lactate levels in ischemic brain (Li *et al.*, 2011a). It also improves blood brain barrier function via PPAR mediated regulation of MMP-9 and TIMP-1 (Cheng *et al.*, 2009), increases functional outcomes, and lessens brain edema (Yousuf *et al.*, 2009). Studies have also demonstrated increased survival (Wang *et al.*, 2014). The neuroprotective effects

of SIRT1 activators appear to be mediated by mitochondrial anti-oxidative, anti-apoptotic, and anti-inflammatory pathways (Shin *et al.*, 2012).

Rodents treated with resveratrol demonstrate decreased mitochondrial swelling, improved mitochondrial membrane potential, and less mitochondria in autophagosomes after cerebral ischemia (Wang *et al.*, 2014). The activity of mitochondrial respiratory complexes I, II and III in the hippocampus of resveratrol treated rodents exposed to middle cerebral artery cerebral ischemia were improved (Yousuf *et al.*, 2009). The mitochondrial/glycolytic master switch in hypoxia, HIF1α, is downregulated in hypoxic glioblastoma cells in a SIRT1 dependent manner, which determines mitochondrial metabolism (Yoon *et al.*, 2014). There is also a marked decrease in mitochondrial cytochrome c release leading to less apoptosis (Yousuf *et al.*, 2009).

Apoptosis associated with ischemic brain injury is associated with multiple pathways influenced by SIRT1. Mechanisms in addition to decreased mitochondrial cytochrome c release include but are not limited to Akt:MAPK:CREB:Bcl-2 (Pugazhenthi *et al.*, 2000), poly(ADP-ribose)polymerase activation and depletion of NAD^+ (Endres *et al.*, 1997; Meli *et al.*, 2003), and p53 (Hernandez-Jimenez *et al.*, 2013). Resveratrol increases serine/threonine kinase Akt (a downstream effector of phosphatidylinositol 3-kinase) and mitogen-activated protein kinases (extracellular signal-regulated kinase1/2 [ERK1/2] and p38) phosphorylation, which is known to be important for cellular survival after stroke (Irving and Bamford, 2002). Their antiapoptotic activity is associated with the transcription factor cyclic AMP response element-binding protein (CREB), which modulates the anti-apoptotic gene Bcl-2 (Pugazhenthi *et al.*, 2000). Furthermore, direct (Wang *et al.*, 2008) and indirect (Wang *et al.*, 2011b) NAD^+ replacement reduces ischemic brain injury. Indirect NAD^+ replacement can be accomplished by nicotinamide phosphoribosyltransferase (NAMPT) administration which increases the NAD^+ salvage pathway via a SIRT1-dependent adenosine monophosphate-activated kinase (Wang *et al.*, 2011b). This results in a SIRT1 dependent decrease in apoptosis and increase in autophagy through the TSC2-mTOR-S6K1 signaling pathway (Wang *et al.*, 2012). Additional SIRT1 dependent anti-apoptotic effects during brain ischemia are associated with deacetylation and inhibition of p53 (Hernandez-Jimenez *et al.*, 2013), apoptotic FOXO proteins (Yang *et al.*, 2013), as well as decreased pro-apoptotic protein Bax (Li *et al.*, 2012).

Protective effects of resveratrol in ischemic brain tissue are also due to decreases in oxidative stress. PGC-1α, a master regulator of antioxidants and a SIRT1 target protein (St-Pierre *et al.*, 2006), regulation is a key method by which resveratrol modulates oxidative stress (Zhu *et al.*, 2010). Antioxidant enzymes that are downstream mediators of PGC-1α include SOD1, SOD2 (Wang *et al.*, 2014), GPx1, and catalase (St-Pierre *et al.*, 2006). Resveratrol treatment also significantly decreases oxidants such as xanthine oxidase, malondialdehyde, hypoxanthine, and xanthine (Li *et al.*, 2011a). Other studies have demonstrated ischemic neuroprotection against oxidative stress in rodents by resveratrol associated with decreased hydroxyl radicals (Lu *et al.*, 2006), modulation of nitric oxide (Tsai *et al.*, 2007), increased mitochondrial glutathione (GSH) and glucose 6-phosphate dehydrogenase (G6PD) (Yousuf *et al.*, 2009), and decreased mitochondrial lipid peroxidation (LPO), protein carbonyl and intracellular H_2O_2 content (Yousuf *et al.*, 2009). In

contrast, SIRT1 mediated deacetylation of Nrf2 (nuclear factor erythroid 2-related factor 2) inhibits its transcriptional activity of antioxidant genes (Kawai *et al.*, 2011). Resveratrol attenuated neuronal death, decreased the generation of ROS, and brought antioxidant and Na(+)K(+)-ATPase activity in the cortex and hippocampus back to normal levels (Simao *et al.*, 2011). Anti-inflammatory targets decreased by SIRT1 include NFκB (deacetylates the p65 subunit at Lys310) (Hernandez-Jimenez *et al.*, 2013; Yeung *et al.*, 2004).

Not only does SIRT1 activation have acute benefits during cerebral ischemia, it also has delayed benefits. Resveratrol increases angiogenesis after brain ischemia by increasing matrix metalloproteinase-2 (MMP-2) and vascular endothelial growth factor (VEGF) levels (Dong *et al.*, 2008). It also preserves cerebral blood flow (Hattori *et al.*, 2015) by deacetylating endothelial nitric oxide synthase, leading to increased nitric oxide production and vasodilation (Hattori *et al.*, 2014).

Inhibition of SIRT1 with sirtinol abolishes ischemic preconditioning-induced neuroprotection in the CA1 region of the rat hippocampus, while resveratrol pretreatment mimics ischemic preconditioning's effects (Raval *et al.*, 2008) (Raval *et al.*, 2006). Both resveratrol and ischemic preconditioning increase brain SIRT1 and reduce uncoupling protein 2 levels (Della-Morte *et al.*, 2009). SIRT1 has also been shown to be instrumental in neuroprotection with ischemia afforded by tetrahydroxystilbene glucoside (Wang *et al.*, 2009), leptin (Avraham *et al.*, 2010), and icariin (Zhu *et al.*, 2010).

Traumatic brain injury is another model in which SIRT1 modulation has shown promise which also involves ischemic processes associated with brain edema limiting blood flow. SIRT1 knockdown is associated with increased traumatic brain injury, whereas SIRT1 overexpression reduces neuronal apoptosis also via the MAPK/ERK pathway (Zhao *et al.*, 2012b). Resveratrol also attenuates early brain injury after subarachnoid hemorrhage through inhibition of NF-kappaB-dependent inflammatory/MMP-9 (Shao *et al.*, 2014). Protection against other neurodegenerative diseases such as Alzheimer's (Kim *et al.*, 2007a), Parkinson's (Wu *et al.*, 2011), Huntington's (Jiang *et al.*, 2012), amyotrophic lateral sclerosis (Kim *et al.*, 2007a), and multiple sclerosis (Tegla *et al.*, 2014) has also been shown with SIRT1.

4.1.1.5.2 Cardiac: In the murine heart, ischemia results in decreased levels of SIRT1, and this decrease is accentuated with aging (Jian *et al.*, 2011a; Lu *et al.*, 2014; Tong *et al.*, 2013). Furthermore, overexpression of SIRT1 in mice results in decreased ischemia reperfusion induced myocardial infarction while decreased expression potentiates the degree of infarction (Hsu *et al.*, 2010). This was associated with 1) an increase of prosurvival molecules such as thioredoxin-1 and Bcl-xL; 2) a decrease of the proapoptotic molecules Bax and caspase-3; 3) decreased oxidative stress with FoxO1 dependent increases in manganese superoxide dismutase. Other studies have demonstrated anti-inflammatory mechanisms of SIRT1 after myocardial ischemia. In mice hearts, SIRT1 decreases the transcriptional activity of the inflammatory cytokine NF-κB through deacetylation of RelA/p65, a subunit of NF-κB (Nadtochiy *et al.*, 2011a). Additionally, the Nampt-SIRT1 pathway stimulates autophagy and prevents cell death during myocardial ischemia (Hsu CP, 2009). Through SIRT1 mediated deacetylation of FoxO1, autophagic proteins such as Rab 7 are

upregulated (Hariharan *et al.*, 2010). SIRT1 also deacetylates and activates the autophagy proteins Atg 5, 7, and 8 (Lee *et al.*, 2008). However, as excessive autophagy during reperfusion could worsen injury, the degree and length of ischemia and reperfusion may affect SIRT1 related changes in survival associated with increased autophagy. Fructose feeding, an intervention known to decrease myocardial ischemia/reperfusion injury in the rat heart (Jordan *et al.*, 2003) appears to act via a SIRT1 dependent mechanism (Pillai *et al.*, 2008), and also reduces the switch in myosin isoforms from α to β myosin heavy chain leading to less cardiac hypertrophy (Mercadier *et al.*, 1981). Ischemic preconditioning, another intervention known to decrease cardiac injury during ischemia/reperfusion (Yang *et al.*, 2010), is also SIRT1 dependent (Nadtochiy *et al.*, 2011b). In mice hearts, SIRT1 overexpression resulted in cytosolic lysine deacetylation and was protective against ischemia-reperfusion injury, while SIRT1 deficient hearts had increased cytosolic lysine acetylation and could not be preconditioned. The SIRT1 inhibitor splitomycin inhibited cardioprotection (Nadtochiy *et al.*, 2011b). The cardiac protection associated with ischemic preconditioning decreases with age, and while SIRT1 also decreases with age, one study suggested these factors are independent (Adam *et al.*, 2013). The cardiac protection in long term caloric restriction also is associated with an increase in nuclear but not total SIRT1 (Shinmura *et al.*, 2008). Interestingly, in a later study, the authors suggested that deacetylation of mitochondrial electron transport chain proteins is responsible for preparing mitochondria for ischemic stress, a task performed by mitochondrial sirtuins, not nuclear sirtuins like SIRT1. Activation of SIRT1 has also been shown to be associated with cardioprotection during ischemia afforded by insulin like growth factor 1 (Vinciguerra *et al.*, 2010) and sildenafil (Shalwala *et al.*, 2014) in mice. SIRT1 is also a direct target of miR-199a, a microRNA which is acutely downregulated during cardiac hypoxia resulting in rapid upregulation of its target, HIF1-α. miR-199a induced activation of SIRT1 destabilizes HIF-1α, resulting in its degradation and countering its cellular effects and associated injury. These data suggest that sirtuins play a central role in multiple known mechanisms of cardioprotection.

Administration of the sirtuin activator resveratrol in the setting of hemorrhagic shock restores SIRT1 activity and improves left ventricular function, cardiac contractility, and survival in resuscitated animals and improves lifespan in non-resuscitated animals (Ayub *et al.*, 2015; Jian *et al.*, 2012) A shift in cellular energetics from oxidative phosphorylation in the mitochondria to glycolysis in the cytosol associated with increased PDK1 (an inhibitor of pyruvate dehydrogenase complex) after severe hemorrhage is reversed with administration of resveratrol (Jian *et al.*, 2014). Resveratrol also abolished the increase in c-MYC levels (Yuan *et al.*, 2009), and decreased PGC-1α, NRF2, and mitochondrial complex I activity associated with hemorrhage (Jian *et al.*, 2014). It holds promise to reverse cardiovascular decline in aged animals with ischemia (Jian *et al.*, 2011a). Consequently, resveratrol induced increases in SIRT1 activity after hemorrhage appear to improve outcomes by affecting mitochondrial function (Jian *et al.*, 2014). Similar experiments on the effect of hemorrhage on rat myocytes have demonstrated that resveratrol inhibits apoptotic pathways, Akt (protein kinase B) dependent inflammation, and injury (Tsai *et al.*, 2012). Consequently, SIRT1 may be a potential target to alleviate cardiovascular decline due to mitochondrial dysfunction in aged animals.

Resveratrol attenuates hepatocyte (Powell *et al.*, 2014; Yu *et al.*, 2010b), intestinal (Yu *et al.*, 2011), lung (Wu *et al.*, 2008), kidney(Wang *et al.*, 2015a) and endothelial (Yu *et al.*, 2010a) injury during hemorrhage induced ischemia. The accumulation and activity of the mitochondrial/glycolytic master switch in hypoxia, HIF1-α, is regulated by SIRT1 in hypoxic hepatocellular (Laemmle *et al.*, 2012), kidney, colorectal, gastric cancer, cervical, lung, fibrosarcoma, glioblastoma and prostate cancer cells (Yoon *et al.*, 2014). Modulating SIRT1 or downstream targets of SIRT1 may allow us to protect from ischemia, reperfusion, and hypoxic injury (Yamamoto and Sadoshima, 2011).

4.1.1.6 Other Sirtuins: Although the majority of studies have focused on SIRT1, a limited number of other sirtuins have been investigated in the setting of hypoxic, ischemic, and reperfusion injury and/or aging. SIRT2, is upregulated by anoxia-reoxygenation in H9c2 cells, while downregulation is protective by decreasing 14-3-3-zeta and translocating the Bcl-2-associated death promoter (BAD) from the mitochondria to the cytosol (Lynn *et al.*, 2008). SIRT3 knockdown is known to result in increased infarct size in murine hearts associated with decreased Cx1 and SOD activity and increased oxidative damage (Porter *et al.*, 2014). SIRT3 also appears to be an important contributor to the pathway by which exercise training results in cardioprotection (Jiang *et al.*, 2014). Increased SIRT3 levels, AMPK phosphorylation, and mitochondrial biogenesis were found in post myocardial infarction rats exposed to aerobic interval training, which is known to improve outcomes (Godfrey *et al.*, 2013; Wan *et al.*, 2007). Resveratrol has also been shown to upregulate SIRT3 expression in the mitochondria resulting in decreased oxidative stress in human vascular endothelial cells (Zhou *et al.*, 2014) and improved cardiac function (Chen *et al.*, 2015). The mitochondrial sirtuin SIRT4 is down-regulated in hypoxia in H9c2 cardiomyoblast cells, and SIRT4 overexpression decreases their apoptosis (Liu *et al.*, 2013b). SIRT5 has also been shown to be a determinant of apoptosis in heart and lung cells (Liu *et al.*, 2013c; Wang *et al.*, 2015b). SIRT6 overexpression in male mice increases life span with associated lower levels of insulin like growth factor 1 (Kanfi *et al.*, 2012). A few studies in the context of cerebral ischemia have been performed. Decreased expression of sirtuin 6 in rats is associated with release of high mobility group box-1 after cerebral ischemia, resulting in inflammation (Lee *et al.*, 2013b). In brain endothelial cells deprived of oxygen, sodium sulfide has a SIRT6 dependent neuroprotective effect (Hu *et al.*, 2015).

4.1.1.7 Role in Aging: Sirtuins influence the aging process and are involved in age related changes (Tissenbaum and Guarente, 2001). This was initially demonstrated with Sir2 in saccharomyces cerevisiae (Kaeberlein *et al.*, 1999), but was also shown in Caenorhabditis elegans (Tissenbaum and Guarente, 2001), drosophila (Whitaker *et al.*, 2013) and in rodents (Kanfi *et al.*, 2012; Satoh *et al.*, 2013). Rafael de Cabo's group recently demonstrated that the SIRT1 activator SRT1720 extends lifespan in adult mice fed a standard diet (Mitchell *et al.*, 2014). They observed delayed onset of age-associated metabolic diseases and improved health in these mice, including inhibition of proinflammatory gene expression in liver and muscle. Sir2 loss of function mutations decrease lifespan in yeast, while increasing Sir2 expression increases lifespan (Kaeberlein *et al.*, 1999) by increasing mitochondrial oxidation and respiration (Lin *et al.*, 2002). Sir2's role in calorie restriction has been questioned by other studies (Kaeberlein *et al.*, 2004; Kaeberlein *et al.*, 2006; Tsuchiya *et al.*, 2006). In *C.*

elegans, a suggested mechanism for Sir2 effect on lifespan is through its impact on the forkhead transcription factor DAF-16, which is typically associated with reduced IGF-1 signaling (Berdichevsky *et al.*, 2006). In this study, overexpression of the *Sir2.1* gene extended lifespan during stress in a 14-3-3 protein dependent manner by increasing DAF-16 activation. Increased autophagy has also been suggested to play a primary role as the life span extending effects of SIRT1 activators are lost in autophagy-deficient *C. elegans* (Morselli *et al.*, 2010). Aged human arteries have decreased SIRT1 expression and activity possibly via cyclin-dependent kinase 5 phosphorylation at the serine 47 residue, suggesting that SIRT1 activators or CDK-5 inhibitors may halt vascular aging (Bai *et al.*, 2014). In the heart, carbonyl modification of SIRT1 is noted to contribute to aging related ischemic intolerance (Gu *et al.*, 2013). SIRT6 in mice affects lifespan by altered phosphorylation levels of major components of IGF1 signaling (Kanfi *et al.*, 2012). Sirtuin activators such as resveratrol have been shown to mimic caloric restriction induced longevity in yeast (Howitz *et al.*, 2003) and animals (Wood *et al.*, 2004). In obese mice on a high calorie diet, resveratrol significantly increased survival and healthspan via increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-I) levels, increased AMP-activated protein kinase (AMPK), increased peroxisome proliferator-activated receptor-gamma coactivator 1 alpha activity, and increased mitochondrial number (Baur *et al.*, 2006). However, non-obese/ standard diet mice do not have increased lifespan but do have improved markers of aging and increased health when treated with resveratrol (Miller *et al.*, 2011; Pearson *et al.*, 2008; Strong *et al.*, 2013). Consequently, given its multiple mechanisms of influencing mitochondrial function in aging and injury, sirtuin activators are a promising way to improve outcomes in elderly individuals sustaining hypoxia or ischemia.

4.1.2 MitoQuinone—MitoQuinone (MitoQ) is a ubiquinone (coenzyme Q10 of the respiratory chain) derivative with a covalent attachment to a lipophilic triphenylphosphonium cation (TPP) through a 10 carbon alkyl chain. Due to significant mitochondrial membrane potential (negative inside), the cationic part of the molecule is directed into mitochondria, while the lipophilic part targets it to the mitochondrial lipid bilayer (Smith *et al.*, 2003). Ubiquinol reduces oxygen radicals, specifically superoxide, and prevents oxidative damage. The respiratory chain then regenerates ubiquinol so it can reduce more radicals. It also has been noted to prevent caspase-independent cell death and prevent lipid peroxidation (McManus *et al.*, 2014). MitoQ accumulates in metabolically active tissues such as the heart, liver, brain, and skeletal muscle (Smith *et al.*, 2003). Fibroblasts pretreated with MitoQ prior to oxidative stress have significantly attenuated free radical production and increased lifespan (Saretzki *et al.*, 2003). They also demonstrated a reversal of telomere shortening. MitoQ prevents hydrogen peroxide-induced apoptosis in mammalian cell culture studies (Kelso *et al.*, 2001) and pretreatment modulates oxidative injury induced by dichlorvos (Wani *et al.*, 2011). Dichlorvos is a synthetic organophosphate insecticide that inhibits neural acetylcholinesterase, mitochondrial complex I, and cytochrome oxidase, resulting in generation of reactive oxygen species. In the study, MitoQ ameliorated dichlorvos induced oxidative stress by decreasing ROS production, increasing MnSOD activity, and increasing glutathione levels. There was also decreased lipid peroxidation, protein oxidation, DNA oxidation, DNA fragmentation, cytochrome c release, and caspase-3 activity. Electron microscopy revealed that MitoQ attenuated dichlorvos induced

mitochondrial swelling, loss of cristae, and chromatin condensation. (Wani *et al.*, 2011). Each of these experiments demonstrates good results in the setting of oxidative stress (not induced by ischemia) and pretreatment. Few studies have been performed evaluating it in the context of ischemia, and even fewer with post injury treatment.

One study evaluated MitoQ in the context of obesity and chronic myocardial ischemia via intermittent left anterior descending artery occlusion. Chronic administration increased obese animals' collateral blood flow and decreased ROS to levels comparable to lean animals (Pung *et al.*, 2012). Another study in a model of cardiac ischemia-reperfusion injury found that feeding MitoQ to rats significantly decreased heart dysfunction, cytochrome c release, caspase 3 upregulation leading to cell death, and mitochondrial damage (Adlam *et al.*, 2005). MitoQ has also been shown to be effective for ischemia/reperfusion injury in the liver (Mukhopadhyay *et al.*, 2012). When animals were pretreated or treated at the time of ischemia, MitoQ dose-dependently attenuated I/R-induced liver dysfunction and damage (manifested by decreased AST, ALT, and histologic changes), but not when given after ischemia and reperfusion. Pretreated animals had significantly improved complex I activity, but unchanged complex II and IV activity. There was less oxidative and nitrative stress response (HNE/carbonyl adducts, malondialdehyde, 8-OHdG, and 3-nitrotyrosine formation), as well as delayed inflammatory cell infiltration, DNA fragmentation, caspase3 activity, and cell death (Mukhopadhyay *et al.*, 2012). MitoQ appears to have significant positive effects for pretreatment of ischemia/reperfusion.

As opposed to pretreatment, one recent study evaluated MitoQ used after ischemic liver injury (Powell *et al.*, 2015). Powell and coworkers used a model of hemorrhagic shock and reperfusion in rats. Arterial blood was withdrawn to a mean arterial pressure of 25 +/− 2 mm Hg for 1 hour before resuscitation and MitoQ was administered intravenously after 30 minutes of ischemia and intraperitoneally after resuscitation. Some positive effects were demonstrated, but results were varied. It decreased markers of inflammation (IL-6 and TNFα) and reduced morbidity. It also increased glutathione activity, but decreased catalase activity, increased liver peroxidation, and did not change superoxide dismutase activity or the degree of liver necrosis. (Powell *et al.*, 2015). MitoQ appears to have varied, but overall beneficial effects when given after hemorrhage.

While no studies of MitoQ's effect on ischemia in the context of aging have been published, MitoQ appears to be able to reverse some age related changes. It has been studied in a model evaluating arterial endothelial function with age (Gioscia-Ryan *et al.*, 2014). In this experiment, acute and chronic administration of MitoQ to aged mice restored ex vivo carotid artery endothelium-dependent dilation by improving nitric oxide bioavailability. There were increases in antioxidants with normalization of age-related increases in superoxide production and oxidative stress. When arterial cells were treated with rotenone, a compound that inhibits the transfer of electrons from iron-sulfur centers in complex I to ubiquinone, MitoQ reversed the age-related increase in endothelial dysfunction (Gioscia-Ryan *et al.*, 2014). Consequently, via a mitochondria dependent mechanism, it may be able to improve blood flow during ischemia, thereby lessening injury in aged individuals, but has not yet been investigated in this manner. One concern about MitoQ is that at higher concentrations. it may act as a prooxidant (Antonenko *et al.*, 2008). Studies have been reported using other

antioxidants such as vitamin E. In a recently published study using mitochondrial targeted vitamin E (Mito-Vit E) and non-targeted vitamin E, Mito-Vit-E exhibited significant efficacy to reduce cytokine and cardiac inflammation in a sepsis model (Zang *et al.*, 2012). Future preclinical and clinical testing of mitochondrial antioxidants may have potential translational significance (Zang *et al.*, 2014).

4.1.3 Estrogens—Rates of ischemic events in women increase after the age of menopause (Rosamond *et al.*, 2007) which raises the question whether increased incidence is due to aging or to hormone status (Cui *et al.*, 2013). At the molecular and cellular level, estrogens appear to decrease mitochondrial-dependent apoptosis (Liou *et al.*, 2010). This study noted that ovariectomied animals that receive 17β-estradiol have decreased ovariectomy-induced cell death. They found that increases in t-Bid, Bax, Bax-to-Bcl2 ratio, Bax-to-BclXL ratio, activated caspase 9, activated caspase 3, anti-apoptotic Bcl2 and Bcl-XL with ovariectomy were countered by estrogen administration (Liou *et al.*, 2010). Mechanistic studies have shown that estrogen receptor beta (ERbeta) is imported into the mitochondria where it affects gene transcription through the interaction with estrogen response elements (ERE) and transcription factors (Simpkins *et al.*, 2008). Conversely, human studies have investigated the influence of estrogen deficiency and/or supplementation on ischemic processes, and there have been conflicting results over the years. Some studies have shown no convincing relationships between postmenopausal status and cardiovascular disease (Atsma *et al.*, 2006), while others have shown a benefit of hormone replacement (Barrett-Connor and Grady, 1998). Another meta-analysis actually showed that hormone replacement therapy increased the risk of coronary artery disease, stroke, and other thromboembolic processes (Nelson *et al.*, 2002). The Women's Health Initiative among 16,608 women found that estrogen plus progestin increased ischemic stroke risk by 44% (Wassertheil-Smoller *et al.*, 2003). After an initial stroke, estrogen alone increases the rate of recurrent fatal stroke and causes an early rise in overall stroke rate in the first 6 months (Viscoli *et al.*, 2001). Another hormone replacement study showed that treated patients had increased coronary events, strokes, and pulmonary emboli. Consequently, while animal and mechanistic studies have been promising, human trials have demonstrated adverse effects (Prentice, 2014).

4.1.4 Calpain inhibitors—Calpains are calcium-dependent, non-lysosomal cysteine proteases whose activation increases ischemia/reperfusion injury (Yousefi *et al.*, 2006). A review (Neuhof and Neuhof, 2014) recently demonstrated that calpain inhibition in animal experiments showed an enhanced tolerance towards ischemia (Neuhof *et al.*, 2003), a reduction of myocardial infarction and reperfusion injury (Hernando *et al.*, 2010; Khalil *et al.*, 2005; Neuhof *et al.*, 2008; Neuhof *et al.*, 2004), and less remodeling (Ma *et al.*, 2012). Other experiments have also shown neuronal preservation during ischemia with calpain inhibition (Nath *et al.*, 2000). Calpain I and 10 are localized in mitochondria. Calpain activation results in cleavage of several mitochondrial proteins including complex I subunits of the electron transport chain (Arrington *et al.*, 2006) and calpain inhibitors restore respiration during ischemia/reperfusion (Neuhof *et al.*, 2003). Calpain inhibitors also prevent mitochondrial membrane permeability transition (Neuhof *et al.*, 2003), attenuate calpain induced cleavage of the pro-apoptotic Bcl-2 family member Bid to an active state (Chen *et al.*, 2001), and prevent calpain from cleaving and releasing apoptosis inducing factor (AIF)

from mitochondria (Chen *et al.*, 2011). It also appears to affect autophagy with aging. When old hepatic cells were pretreated with a calpain inhibitor, there was less Atg4B (autophagy related protein) loss, increased autophagy and mitophagy, and decreased cell death (Wang *et al.*, 2011a). The authors suggested that more mitophagy results in timely clearance of injured or injury prone mitochondria leading to better outcomes with ischemia/reperfusion in aged individuals (Wang *et al.*, 2011a). Given that calpain has multiple targets for cleavage that have many different functions, inhibition of specific downstream targets affecting ischemia/reperfusion tolerance could help prevent the increased injury associated with aging.

4.1.5 Melatonin—Melatonin, the chief secretory product of the pineal gland that functions as a regulator of sleep, circadian rhythm, and immune function, is also a direct free radical scavenger and indirect antioxidant (Poeggeler *et al.*, 1994). It been shown to reduce oxidative stress by quenching the hydroxyl radical (Li *et al.*, 1997), superoxide anion radical, singlet oxygen, peroxyl radical, and the peroxynitrite anion (Mayo *et al.*, 2005). It stimulates superoxide dismutase, glutathione peroxidase, glutathione reductase, and glucose-6-phosphate dehydrogenase and inhibits nitric oxide synthase. It also stabilizes cell membranes (Rodriguez *et al.*, 2004), modulates the gene expression of protective enzymes that reduce apoptosis such as Bcl2 (Ling *et al.*, 1999), inhibits autophagy (Zheng *et al.*, 2014), and decreases lipid peroxidation (Wakatsuki *et al.*, 1999), and prevents mitochondrial inhibition thereby promoting ATP production (Reiter *et al.*, 1998). Melatonin deficient rats have been shown to have increased brain damage after stroke (Manev *et al.*, 1996), while administration of melatonin reduces neuronal injury (Cho *et al.*, 1997) and increases survival (Cuzzocrea *et al.*, 2000a). In neonatal hypoxia/ischemia, melatonin preserves sirtuin 1 expression thereby resulting in neuroprotection. Preadministration of melatonin attenuated renal ischemia/reperfusion injury in rats (Ahmadiasl *et al.*, 2014) and decreases hepatic ischemia/reperfusion injury (Kireev *et al.*, 2012). Melatonin is noted to decrease with age which may be a factor in increased oxidative damage in the elderly (Reiter *et al.*, 1998).

4.1.6 Hydrogen Sulfide (H_2S)—Hydrogen sulfide (H_2S) is historically known as a toxic environmental pollutant with various deleterious effects on organ systems (Beauchamp *et al.*, 1984). However, H_2S along with nitric oxide (NO) and carbon monoxide (CO) is increasingly recognized as an endogenously produced gaseous signaling molecule (Lowicka and Beltowski, 2007). It is now recognized as an antioxidant that modulates glutathione levels (Kimura and Kimura, 2004; Yang *et al.*, 2011) and can antagonize apoptosis in the setting of ischemia and reperfusion (Biermann *et al.*, 2011; Elrod *et al.*, 2007). Endogenous H_2S levels are markedly reduced by hypoxia, and over-expression of cystathionine-beta-synthase (CBS), the main producer of hydrogen sulfide in the brain, as well as administration of Na_2S prevents hypoxia induced cell apoptosis via the K(ATP)/PKC/ERK1/2/Hsp90 pathway (Tay *et al.*, 2010). In oxygen and cortical neuron glucose deprivation/reperfusion experiments, H_2S reduces intracellular ROS, caspase 3 activation, damage of mitochondrial membrane potential, leading to decreased apoptosis (Luo *et al.*, 2013). It has also been shown to be effective in cardiac H9c2 cells exposed to chemical hypoxia by inhibiting ROS-mediated activation of ERK1/2 (Dong *et al.*, 2012). Another study found that aged healthy mice have high levels of CBS and suggested that maintenance (and increase) of CBS levels may sustain cortical function, preclude neuronal loss, and

extend survival (Bruintjes *et al.*, 2014). Other studies have corroborated their suggestions, finding that H2S prolonged survival in C. elegans (Qabazard *et al.*, 2013; Qabazard *et al.*, 2014). Consequently, modulation of H2S may be a viable strategy to maintain mitochondrial function and improve outcomes in aging individuals exposed to hypoxic ischemic injury.

Ginkgo biloba extract is a free radical scavenger that may counter the increased oxidative stress with aging.

4.1.7 Methylene Blue—Methylene blue (MB) is a heterocyclic aromatic compound that is FDA-approved for methemoglobinemia and an antidote to cyanide poisoning. MB is known to improve mitochondrial function (Atamna *et al.*, 2008; Tokumitsu and Ui, 1973) by increasing the utilization of oxygen and increasing complex IV activity. It also is an alternative electron carrier that shuttles electrons between NADH and cytochrome *c* (cyt *c*) so that electrons are rerouted with complex I and III inhibition thereby attenuating ROS overproduction. Its neuroprotective effects have also been attributed to mitophagy (Di *et al.*, 2015), stimulation of HIF-1α (Ryou *et al.*, 2015), and improved cerebral metabolic and hemodynamic function (Lin *et al.*, 2012). MB significantly decreases infarct volume after middle cerebral artery occlusion in animal models (Di *et al.*, 2015; Shen *et al.*, 2013). Given its current use in clinical settings and known side effects, it may easily be a promising translational treatment for the mitochondria dysfunction seen with aging in ischemia (Wen *et al.*, 2011).

4.2 Other Antioxidants

4.2.1 Tempol—Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) is a nitroxide compound that has been extensively studied as an antioxidant as it functions as a superoxide dismutase mimetic (Wilcox, 2010). Pretreatment with tempol has been shown to attenuate ischemia/reperfusion damage in the kidney (Chatterjee *et al.*, 2000; Patel *et al.*, 2002), heart (McDonald *et al.*, 1999), liver (Sepodes *et al.*, 2004) and brain (Cuzzocrea *et al.*, 2000b). It has also demonstrated protection against shock from hemorrhage (Mota-Filipe *et al.*, 1999). Additionally, it appears to be effective when given intravenously at the time of reperfusion as it reduced lipid peroxidation and the infract size in the brain. However, if given 15 minutes before reperfusion, it was not effective (Kato *et al.*, 2003).

Tempol appears to specifically target mitochondrial reactive oxygen species. When administered orally in an experiment with cardiac cells, tempol prevented O_2^- production by mitochondrial complex 1 when tumor necrosis factor alpha was administered (Mariappan *et al.*, 2009). It has also been shown to prevent angiotensin II from stimulating mitochondrial ROS (Kimura *et al.*, 2005). Tempol attenuates ROS and prevents hepatic mitochondrial damage and dysfunction associated with increased angiotensin II production in renin-2 transgenic rats (Wei *et al.*, 2009). However, it did not preserve mitochondrial function in a model of spinal cord injury where Ca^{2+} overload was the major factor contributing to mitochondrial dysfunction rather than ROS (Patel *et al.*, 2009).

Efforts have been made to target tempol to mitochondria by complexing it with ubiquinone and gramicidin S with generally good results although one study showed no difference (Dessolin *et al.*, 2002). Studies have shown increased mitochondrial uptake, less activation

of mitochondrial uncoupling proteins (Murphy *et al.*, 2003), less complex I dysfunction (Esplugues *et al.*, 2006), decreased H_2O_2-induced apoptosis (Kelso *et al.*, 2001), and less ischemia–reperfusion injury (Esplugues *et al.*, 2006) when tempol is conjugated with ubiquinone. Conjugation with gramicidin S also enhances tempol concentration in mitochondria and decreases apoptosis (Jiang *et al.*, 2007; Wipf *et al.*, 2005).

Tempol has been also been effective in reversing changes associated with aging. Tempol increases the lifespan of *Drosophila melanogaster* (Izmaylov and Obukhova, 1996), and mice fed tempol from birth live significantly longer than controls (Mitchell *et al.*, 2003). By lowering oxidative stress, tempol has been shown to normalize the age-related decline in dopamine receptor function (Fardoun *et al.*, 2006). Additionally, the altered regulation of vascular tone with aging is countered by tempol, as it has been shown to restore the decline in nitric oxide (NO) induced inhibition of cardiac O_2 usage (Adler *et al.*, 2003) and restore the decreased arteriolar response to endothelial derived relaxing factor (EDRF) seen with aging (Durrant *et al.*, 2009; Lesniewski *et al.*, 2009; Mayhan *et al.*, 2008; Payne *et al.*, 2003). It appears to function in aged animals by substituting for superoxide dismutase, an antioxidant whose expression is decreased with aging (Lund *et al.*, 2009). Therefore, tempol likely has a role in preventing the increased injury seen with aging during hypoxic ischemic injury (Wilcox, 2010), but its therapeutic value, especially in human studies, remains unclear.

4.2.2 Schisandrin B—Schisandra fruits have been traditionally used in East Asia for numerous diseases, and Schisandrin B, a dibenzocyclooctadiene derivative from Schisandra fruit extract, has been shown to be protective during ischemia to the brain (Lee *et al.*, 2012), liver, and heart (Chiu *et al.*, 2006). During focal cerebral ischemia in rats Schisandrin B administered before and after ischemia reduced infarct volumes up to 53.4% with reduced expression of TNF-α and IL-1β, and degradation of MMP-2 and MMP-9 (Lee *et al.*, 2012). Another study noted that Schisandrin B improved glutathione, alpha-tocopherol and Mn-superoxide dismutase levels, while preserving mitochondrial structure and function (Ca2+ loading, cytochrome c release, and permeability transition) (Chen *et al.*, 2008). Improvement in antioxidant status is noted with chronic administration (Chiu *et al.*, 2006). Following brain anoxia in mice another study noted decreased swelling and disintegration of brain mitochondria with improved membrane fluidity and increased production of cytosol glutathione-peroxidase (Xue et al., 1992). Protection has been demonstrated in both young and aged animals (Chiu et al., 2006). Therefore, by improving cerebral mitochondrial antioxidant status, aged individuals may be protected against ischemia/reperfusion injury with administration of Schisandrin B, although human studies are lacking.

4.2.3 Uric Acid—Uric acid is a well-known antioxidant produced through the metabolic breakdown of purine nucleotides such as ATP. Uric acid protects cultured rat hippocampal neurons against cell death through suppression of oxygen and nitrogen radical accumulation (hydrogen peroxide and peroxynitrite), stabilization of calcium homeostasis, preservation of mitochondrial function, and by decreasing exposure to the excitatory amino acid glutamate and the metabolic poison cyanide (Yu *et al.*, 1998). It is neuroprotective in rats one hour following reperfusion in cerebral ischemia and improves behavioral outcome (Yu *et al.*,

1998). Uric acid has low solubility in water resulting in pathogenic processes such as gout and kidney stones. Consequently, soluble analogs have also been synthesized, studied, and shown to be neuroprotective in ischemic brain injury in mice (Haberman *et al.*, 2007). Dietary restriction, an intervention known to increase ischemic tolerance, has also been shown to increase uric acid levels thereby augmenting the anti-oxidative defense system with aging (Chung and Yu, 2000).

4.2.4 Alpha-phenyl-tert-butyl-nitrone (PBN)—PBN is a free-radical spin trap that also inhibits cyclooxygenase-2 activity and nitric oxide synthase (iNOS) (Durand *et al.*, 2008). In aging rat brain following cardiac arrest and resuscitation, the antioxidant alpha-phenyl-tert-butyl-nitrone (PBN) improves mitochondrial respiratory function and reduces lipid peroxidation (Xu *et al.*, 2008). A follow up study in also in aged rats demonstrated improved overall survival and increased hippocampal CA1 neuron survival with PBN treatment (Xu *et al.*, 2010).

4.2.5 Mannosylated Liposomal Cytidine 5′ Diphosphocholine—Cytidine 5′ diphosphocholine (CDP-Choline), an intermediate in the generation of phosphatidylcholine from choline, has some studies in human trials illustrating its effectiveness in stroke (Warach *et al.*, 2000). Some studies have even reported substantially reduced frequencies of death and disability (Saver, 2008) although a large randomized placebo controlled study failed to show any difference (Davalos *et al.*, 2012). One challenge is drug delivery, as CDP-choline is frequently broken down after administration and must reform. An alternative strategy involves conjugating the drug to mannosylated liposomes. Liposomes are known to be an effective drug carrier especially during ischemia and reperfusion (Fresta and Puglisi, 1997) and mannose receptors expressed on brain cells facilitate endocytosis (Regnier-Vigouroux, 2003). CDP-Choline in a mannosylated liposome delivery system exerts increased protection against global cerebral ischemia and reperfusion induced mitochondrial damage in young and aged rats (Ghosh *et al.*, 2010). Treatment decreased membrane lipid peroxidation, reactive oxygen species, and mitochondrial cytochrome c release, while increasing superoxide dismutase and catalase levels.

4.2.6 Luteolin—Luteolin is a polyphenol compound found in many fruits such as Perilla frutescens, vegetables, and herbs (Zhao *et al.*, 2010) that possesses anti-inflammatory, antiallergic, anticarcinogenic, and immune-modulating properties (Zhao *et al.*, 2012a). It scavenges superoxide radicals using its polyphenolic hydroxyl groups and has been shown to reduce inhibition of mitochondrial function, decrease reactive oxygen species, and increase catalase and GSH levels in primary neurons treated with H_2O_2 (Zhao *et al.*, 2012a). Liposome-encapsulated luteolin administered after ischemia also prevents ischemia-reperfusion injury with middle cerebral artery occlusion model in rats. Treated animals demonstrated decreased symptom scores, improved balance, and behavioral improvement (Zhao *et al.*, 2011).

4.2.7 Selenium Compounds—Diphenyl diselenide $(PhSe)_2$ is a potent antioxidant that exhibits glutathione peroxidase-like activity and decomposes H_2O_2 or other radicals. $(PhSe)_2$ administered 30 minutes prior to bilateral common carotid artery occlusion in rats

improved cerebral levels of malondialdehyde (MDA), ROS, nitrate/nitrite and antioxidant defenses (catalase and superoxide dismutase), proinflammatory cytokines, tissue damage markers (creatine kinase and α-1-acid glycoprotein), and histological outcomes compared to untreated rats exposed to I/R (Bruning *et al.*, 2012). Another study in which animals were treated one hour after ischemia noted improved neurological testing, decreased collapse of mitochondrial membrane potential, improved mitochondrial complex I (NADH dehydrogenase) activity, decreased mitochondrial swelling, improved GSH/GSSG levels, improved MnSOD activity, improved glutathione peroxidase activity, and decreased Hsp70 gene expression (Dobrachinski *et al.*, 2014). While selenium compounds effect on hypoxia in aged animals is not known, studies have shown that selenium compound supplementation in conjunction with swimming improves pro and anti-inflammatory cytokine profiles, memory and spatial learning in aged rats by increasing phosphorylated cAMP-response element-binding protein (CREB) levels (Cechella *et al.*, 2014; Leite *et al.*, 2015).

5 Conclusions

Mitochondria play critical functions in the response to hypoxia, ischemia and reperfusion. Aging results in increased apoptosis, dysregulated autophagy, increased disruption of the mitochondrial permeability transition pore, and exacerbated injury following hypoxic-ischemic insults. Aging aggravates mitochondrial functional decline following hypoxic-ischemic injury and worsens clinical outcomes. The decreased ATP production, increased ROS and mitochondrial-glycolytic shift in cellular energetics are controlled by master regulators such as HIF-1α, PGC-1α, and c-MYC. Age associated decline in NAD+ contributes to substrate starvation leading to decreased SIRT1 activity and a pseudohypoxic state. Preventative and therapeutic pharmacologic agents such as STACs and resveratrol, tempol, mitoquinone, cationic plastoquinone derivatives, estrogens, as well as apoptosis inhibitors, have been shown to be effective in experimental models of neuronal ischemia. Mitochondrial transfer to cells with damaged mitochondria from donor cells via nanotubular tunnels is an emerging area that require further studies to establish functional relevance in vivo. Translational research is needed for most of these potential therapies to test the feasibility to transition from bench to bedside. Nevertheless, investigations in aging and injury converge on biological mechanisms vital to bioenergetics underlining the significance of mitochondrial functional modulation not only on the effects of ischemia on the nervous system, but also in other organ systems and pathways that determine health and disease.

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Abbreviations (alphabetized list)

mtDNA	mitochondrial DNA
PPAR	peroxisome proliferator-activated receptor
PGC	peroxisome proliferator-activated receptor gamma, coactivator

TBI	traumatic brain injury
TFAM	transcription factor A mitochondrial
ROS	reactive oxygen species
ERR	estrogen receptor related receptor
NRF	nuclear respiratory factor
SRT1	sirtuin 1
Drp1	Dynamin-related protein 1
Fis1	Fission 1
NMN	nicotinamide mononucleotide

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Highlights

- Nuclear-mitochondrial cross talk is important in maintaining mitochondrial structure and function.
- Metabolic master regulators, c-MYC and HIF-1, modulate mitochondrial function and cell fate following hypoxic/ischemic injury.
- Aging exacerbates hypoxic/ischemic injury and mitochondrial functional impairment.
- AMPK-SIRT1 mediated energy sensing is important in energy homeostasis following hypoxic/ischemic injury.
- Post translational regulation of molecular mediators play a critical role in the control of glycolytic-mitochondrial energy axis in response to hypoxic/ischemic conditions.

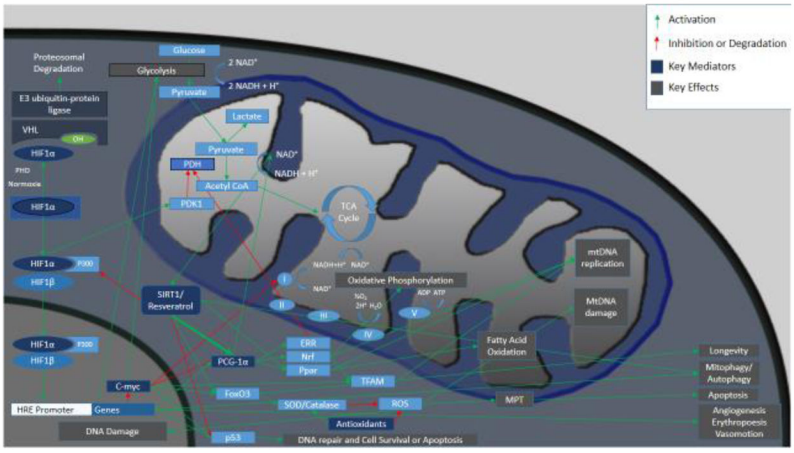

Figure 1. Critical molecular mediators in hypoxia/ischemia

HIF-α is a critical modulator of hypoxic response. SIRT1 deacetylates Lys674 of HIF-1α, which inhibits P300 binding and decreases HIF-1α signaling. During hypoxia, SIRT1 is suppressed consequent to decreased NAD^+, and facilitates HIF-1 signaling (Lim *et al.*, 2010). HIF-1α induces gene transcription leading to activation of many mediators including glycolytic enzymes, and also activates pyruvate dehydrogenase kinase 1 (PDK1) which inhibits pyruvate dehydrogenase (PDH) leading to inhibition of mitochondrial oxidation. PGC-1α activation leads to NRF, ERR, and PPAR activation, which increase mitochondrial function and biogenesis.

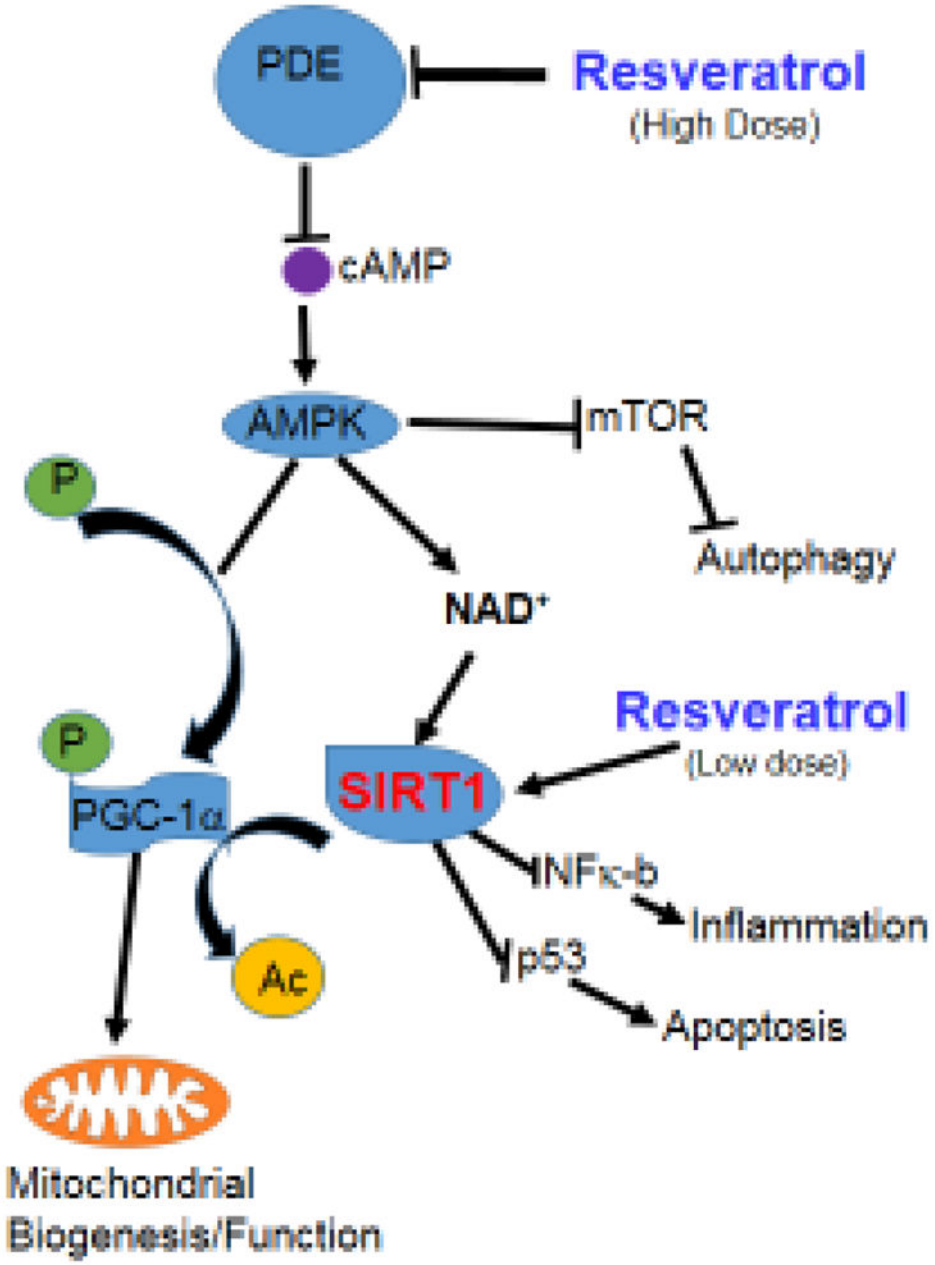

Figure 2. SIRT1-AMPK axis in resveratrol mediated metabolic regulation

Resveratrol has been demonstrated to be an allosteric activator of SIRT1. (Price et al, 2013). Resveratrol may also act through phosphodiesterase (PDE) leading to AMPK activation, increased NAD+ and phosphorylation of Pgc-1α (Park et al, 2012). SIRT1 deacetylates Pgc-1α. Phosphorylated and deacetylated Pgc-1α augments mitochondrial biogenesis and function. The pathway of action of resveratrol has been suggested to be dose-dependent (Price et al, 2013). Among other functions of SIRT1 include deacetylation and inactivation of Nfkb and p53. P= phosphate group, Ac= acetyl group.