12-13-2013

Mitochondrial Dysfunction and Reactive Oxygen Species in Neurodegeneration

Leah Farina
Western Michigan University, farinaleah@yahoo.com

Follow this and additional works at: http://scholarworks.wmich.edu/honors_theses
Part of the Biology Commons

Recommended Citation
Mitochondrial Dysfunction and Reactive Oxygen Species in Neurodegeneration

Leah K. Farina

Lee Honors College

Western Michigan University
Abstract

Neurodegeneration leads to the loss of normal anatomy and physiology of the neuronal system in a human body. The hallmark of most neurodegenerative diseases is abnormal folding and accumulation of proteins within neuronal cell bodies that is not present in healthy people. These changes in normal protein metabolism often lead to neuronal cell death and failure of the affected regions of the central nervous system. Abnormal protein accumulation may be attributed to dysfunctional mitochondria and damage by reactive oxygen species. In addition to causing altered protein accumulation, dysfunctional mitochondria and an excess of reactive oxygen species also lead to errors in glucose metabolism, which create problems in energy production and insulin signaling. The problems in these processes are targets for therapeutic techniques to find treatments for neurodegeneration and include insulin sensitizing compounds, and antioxidants. No treatments have yet been found successful to rid a person of neurodegeneration completely; however, progress has been made towards targeting the mitochondria and reactive oxygen species to halt the progress of neurodegenerative diseases in humans.
Mitochondrial Dysfunction and Reactive Oxygen Species in Neurodegeneration

Introduction

Neurodegenerative diseases cause death of neuronal cells to the point of progressive pathological disease. How these neurons die is still a question in deep study, although many breakthrough findings have been made. There are many different types of neurodegenerative diseases including but not limited to Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS). These diseases affect millions of people worldwide (Cai et al., 2012). As the two most prevalent of all neurodegenerative diseases in the United States, Alzheimer's disease affected 5.4 million people and Parkinson's disease affected 1.5 million people on average last year. Huntington's disease is rarer, with 30,000 people in the United States showing symptoms of it last year (Pal, 2012). However, since the average life expectancy of the population is rising, and neurodegenerative disease diagnoses increase with age, the number of neurodegenerative cases has also been rising with the elderly population (Forman et al., 2004).

Alzheimer's disease is characterized by plaques made of amyloid beta protein and neurofibrillary tangles of overly-phosphorylated tau protein. These plaques cause clinical symptoms including dementia, or cognitive decline. In Parkinson's disease, there is a loss of neurons in the substantia nigra, with inclusions called Lewy bodies that are accumulated α-synuclein and ubiquitin proteins. The loss of these motor neurons causes rigidity and tremors in the human body suffering from Parkinson's. Huntington's disease is characterized by a “loss of long projection neurons in the cortex and striatum” (Lin & Beal, 2006). There is also an irregular polyglutamine addition in the N terminal of the huntingtin protein in this disease (Charvin et al., 2005). A person with Huntington's disease develops signs of psychiatric problems and dementia from these physiological problems developing in the brain. Amyotrophic Lateral Sclerosis is known for the degeneration of motor neurons in the cortex,
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

brain stem, and spinal cord along with accumulations of mutated copper and zinc superoxide dismutase. Somebody with ALS will show progressive weakness and atrophy (Lin & Beal, 2006). All of these diseases act in different ways to affect the body, but it is believed that they all are initiated in similar ways.

There are reasons to believe that the mitochondria play a role in the degeneration of neurons in these diseases. The mitochondria play a big role in how all cells function properly. Mitochondria contain its own DNA (mtDNA), and run many of the human body's energy metabolic systems like the Krebs cycle (also known as the citric acid cycle) and the electron transport chain to make adenosine triphosphate (ATP). This ATP lets the body function by providing energy to our cells, tissues, and organs. The circular mtDNA accumulates many mutations as a person ages (Linnane et al., 1989; Vieira & Kroemer, 1999). These mutations may lead to mitochondrial dysfunction and is hypothesized to cause serious trouble in the human body including the initiation and progression of neurodegenerative diseases.

Reactive oxygen species (ROS) are known to accelerate aging and to cause damage to many cells in the body, including neurons. When the body metabolizes oxygen in oxidative phosphorylation, mitochondria create reactive oxygen species. Reactive oxygen species are molecules with an unpaired electron and as a result, are very reactive and damaging to our cells (Halliwell, 1992). These molecules are “redox reactive” and are able to affect different cell components in many ways. For example, ROS are able to oxidize proteins, which could negatively affect active sites on enzymes, not allowing the substrate to properly bind. ROS could change the shape of proteins completely, which would also have an effect on how the protein functions. These molecules can also cause peroxidation of lipids, which causes degradation of fatty acids and lipids. These components make up the plasma membranes and organelle membranes of the cells. Once lipid peroxidation takes place these membranes are likely to
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

become seriously damaged. This could cause detrimental effects to the cell for the plasma membrane protects the cell from many potential dangers. ROS also directly oxidize DNA and cause mutations in some cases (Andersen, 2004). This is why the reactive oxygen species have been closely linked to neurodegeneration.

The mitochondria and reactive oxygen species together can lead to problems such as a faulty glucose metabolism and decreased ATP. Several steps in these important metabolic processes are targets for therapeutic intervention to treat neurodegenerative disorders. In order to understand neurodegenerative disorders effectively, it is important to recognize that there may be multiple etiologies and several different complex pathways that lead to the progression of the various forms of these ailments.

Mitochondrial Dysfunction and Neurodegenerative Diseases

The mitochondria are the most important and essential organelles for energy production and cellular metabolism. The mitochondria are critical energy conservation centers in human cells. Through oxidative phosphorylation they create ATP with the food that humans eat and the oxygen that humans breathe (Rego & Oliveira, 2003). ATP is the energy currency that every cell needs in order to carry out processes that are needed to allow an organism to survive. Some cells, like muscle cells, can survive without a lot of mitochondria, because they can survive on the “glycolytic oxidation of stored glucose molecules” (Fiskum et al., 1998), however, this is not the case with neurons. Neurons need the mitochondria to be fully functional because they are highly metabolically active and do not have a backup system as some other cells do for energy production (Fiskum et al., 1998).

When mitochondria in neurons do become dysfunctional, many problems can occur. One way the mitochondria become damaged and dysfunctional is through ROS. ROS cause a decrease in the functionality of many needed mitochondrial enzymes. These enzymes include pyruvate dehydrogenase
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

and cytochrome oxidase. The cell counts on these enzymes for both the Krebs cycle and glucose metabolism and once deficient in these enzymes, the mitochondria become dysfunctional (Colca & Feinstein, 2012). The stress associated with enzyme malfunctions in metabolic pathways may also account for some mutagenesis in the mitochondrial DNA. Another way mitochondria are proposed to become dysfunctional is through mutations accumulated over a person's lifetime. The mtDNA is known for “large scale deletions or point mutations” that cause adverse effects to the mitochondria function by negatively affecting energy production processes (Lin & Beal, 2006).

Once some of the mitochondria are not working, less ATP are produced because oxidative phosphorylation becomes less prevalent in a given cell. With less ATP, fewer processes in the cell take place. These processes include autophagy and lysosomal degradation. Unfortunately, these processes are necessary for getting rid of proteins that are folded improperly and for getting rid of many other waste products in the cell. When the mitochondria do not make enough ATP to perform these processes, the cell cannot dispose or recycle these deformed proteins and they accumulate and aggregate.

In addition, if the cell no longer has enough ATP, it cannot perform normal cell-to-cell communication via the synapses (Reddy et al., 2011; Colca & Feinstein, 2012). This is an important function for the nervous system because it keeps the brain in communication with the rest of the body and the external environment. This loss of critical information exchange by the central nervous system leads to the visible signs and progressive pathology of neurodegenerative disease (MENA report, 2013).

The mitochondria in a cell are also known for keeping calcium levels stable, as an excess in calcium can lead to cell death. (Castellani et al., 2002) This means that dysfunction in the mitochondria is able to cause spikes in calcium levels, for it no longer has sufficient ATP to maintain membrane potential to keep the cells in a state of homeostasis. (Rego & Oliveira, 2003). When calcium levels
fluctuate in the cell, apoptosis is usually initiated because more calcium creates increased sensitivity to “apoptotic stimuli” (Rizzuto et al., 2003). These apoptotic stimuli include the Bax and Bcl proteins, which activate the opening of the mitochondrial permeability transition pore and eventually this leads to cell death.

Studies have shown that with dysfunctional mitochondria comes an increase in reactive oxygen species that are produced in the mitochondria. This may be due to an alteration in the electron transport chain which causes defects in the enzymatic complexes, resulting in the release of an excess of ROS (Benzi & Moretti, 1995). Reactive oxygen species endanger the neuron by causing damage to membranes, proteins, and nucleic acids. Not only do reactive oxygen species cause more damage to the mitochondria, but they also initiate apoptosis, programmed death of the cell. Apoptosis is a very orderly process in the cell, and it happens only in extreme cases when the cell knows it cannot be repaired. When mitochondria go through dysfunctional changes, there is a very good chance the cell will go through apoptosis. One trigger of apoptosis is through the opening of the mitochondrial permeability transition pore (MPT) on the inner membrane of the mitochondria (Castellani et al., 2002; Vieira & Kroemer, 1999). The MPT is activated during a decrease in mitochondrial function characterized by an increase in reactive oxygen species, a decrease in ATP production, and an associated rise in calcium. The opening of this pore induces the release of the cytochrome c protein which activates caspases (Castellani et al., 2002) causing apoptosis (Colca & Feinstein, 2012). The sensitivity of the mitochondrial permeability transition pore to increased calcium has been shown to be increased by oxidative stress. Therefore dysfunctional mitochondria with increased ROS are creating an opportune environment for apoptosis through the opening of the MPT pore (Pastrushev et al., 2004). Figure 1 depicts some ways that neurons go through cell death with details of apoptosis and other pathways that lead to cell death.
As seen by all of these examples, any form of mitochondrial dysfunction is very harmful to the neurons in the brain and it leads to neurodegeneration. It elicits the process of protein accumulation and aggregation in many ways. There have been studies done that show that protein accumulation can also arise inside the mitochondria. A good example of this would be the amyloid precursor protein in Alzheimer's disease. This protein has been shown to accumulate inside the protein channels of the mitochondria, causing damage to the mitochondria (Devi et al., 2006). There have been similar findings with an array of proteins in various neurodegenerative diseases, showing that protein accumulation inside the mitochondria leads to dysfunction and further destruction of neurons (Kwong et al., 2006; Cho et al., 2010; Colca & Feinstein, 2012). Figure 2 below shows how accumulation of different pathogenic proteins like the α-synuclein protein and the parkin protein affect mitochondria.
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

Figure 2- (Knott et al., 2008)

It is unknown as to whether the dysfunctional mitochondria cause the protein aggregation and accumulation, or if the protein aggregation causes the mitochondria to become dysfunctional. There have been clues and evidence to support each claim but it is believed that the combination of both advances neurodegeneration.

Oxidative Stress and Neurodegenerative Diseases

Reactive oxygen species and reactive nitrogen species cause unfavorable effects to all cells in the body, especially the neurons in the brain (Multhaup et al., 1997). The brain does not regenerate as other parts of the body do, and it is very active metabolically, therefore very susceptible to injury by oxidative stress (Andersen, 2004). Many of the reactive oxygen species are made in the mitochondria. These species usually include “hydroxide and superoxide radicals and hydrogen peroxide” (Rahman et al., 2012). Nitric oxide (NO) is made by the N-methyl-D-aspartate glutamate receptors in the nervous system. When these receptors are overly activated, this initiates a “calcium influx” making nitric oxide...
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

and other reactive oxygen species (Rahman et al., 2012). Usually in the healthy brain a normal amount of reactive oxygen species is not harmful, but in fact it is needed. Reactive oxygen species are involved in cell signaling in small amounts (Calabrese et al., 2007). However, in the diseased aging brain, reactive oxygen species accumulate and cause protein accumulation and aggregation. In addition to the increased production of reactive oxygen species, there is a decreased production of antioxidant agents such as the enzymes “superoxide dismutase, glutathione peroxidase, and glutathione reductase” (Andersen, 2004) in the brains of persons with neurodegeneration (Benzi & Moretti, 1995).

The ROS and NOS are able to directly cause protein accumulation by destroying chaperone and proteasomal processes. The function of the molecular chaperone is to find misfolded proteins and help to fold them properly. The ubiquitin-proteasome-system (UPS) functions to find and degrade proteins that are misfolded. Without these two processes, misfolded proteins would accumulate, and eventually aggregate. A number of studies have shown that NO seems to have destructive effects on the chaperones and UPS proteins (Nakamura & Lipton, 2007). A process called S-nitrosylation occurs on chaperone proteins and specific UPS proteins known as “protein-disulfide isomerase, glucose-regulated protein 78, and heat shock proteins” (Taylor et al., 2002) to cause them to become debilitated. This process adds an “NO group to a cysteine thiol/sulfhydryl to make an S-nitrosothiol” (Rahman et al., 2012). These proteins no longer work as they are supposed to; either fixing misfolded proteins or degrading them, therefore causing a protein accumulation.
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

If not causing protein aggregation directly, reactive oxygen species accumulate to create damage elsewhere in the cell to contribute to the cause of neurodegeneration. ROS made in the mitochondria from oxidative phosphorylation are able to accumulate and damage the mitochondrial DNA (mtDNA) itself. Once mutated, mtDNA causes more dysfunction in oxidative phosphorylation and the mitochondrial structure, leading to a larger accumulation of ROS. It is known as the vicious cycle of the mitochondria, and once it starts, it does not stop. Antioxidant functions are impaired at this point in a neurodegenerating cell body so there is no defense against this cycle as it takes over the brain (Fukui & Moraes, 2008). Damage to the mitochondria will cause a depletion of ATP, an influx in calcium, and in most cases the opening of the mitochondrial permeability transition pore leading to apoptosis. Figure 3 below illustrates the viscous cycle of the mitochondria, and what it does to the neuron.

Figure 3- (Schue A.)

Reactive oxygen species not only cause direct protein accumulation and mitochondrial
dysfunction, but can also cause glial cell activation and inflammation. (Salminen et al., 2012) When glial cells detect damage induced by reactive oxygen species, the microglia are stimulated to activate genes that are involved in the release of cytokines, NO, and NADPH oxidase (Andersen 2004; Lobsiger & Cleveland, 2007). The cytokines include proinflammatory interleukins-1, and -6, and tumor necrosis factor-α (TNF-α). These things, in turn, cause damage to the neurons by over-inflammation, tissue damage, and the production of more reactive oxygen species. NO has detrimental effects on the cell and once NO is mixed with the superoxide anion reactive oxygen species, peroxynitrite (ONOO-) is formed which can nitrosylate proteins causing them to become deformed and accumulated. (Zhang et al., 2012). This form of reactive nitrogen species is thought to be a major part of the β-amyloid protein toxicity in Alzheimer's disease (Andersen, 2004; Qin et al., 2002).

Certain glial cells known as astrocytes have a specific function in neurodegeneration as well. Astrocytes are the cells responsible for glutamate, an excitatory factor of the central nervous system. Over activation of the astrocytes causes altered glutamate handling, leading to abnormal excitatory processes and calcium signaling waves. (Lobsiger & Cleveland, 2007; Malta et al., 2012). Increased activation of astrocytes leads to increased chances of death of dopaminergic neurons as seen in the pathogenesis of Parkinson's disease (Andersen, 2004).

The reactive oxygen species created throughout many processes in neurodegeneration have deleterious effects on the central nervous system. The ROS are an initiating factor in the process of apoptosis. These molecules can cause direct damage to open the mitochondrial permeability transition pore which activates transduction pathways, kinases and releasing cytochrome c. ROS can also have damaging effects on things like RNA and DNA. The damage done to RNA and DNA can then force a cell into programmed cell death. Reactive oxygen species activate astrocytes to cause glutamate excitotoxicity. With this comes a cascade of events causing programmed cell death through the
activation of NMDA receptors. This causes an influx of calcium, production of nitric oxide (NO), and depolarization of the mitochondrial membrane. This then causes the mitochondria to produce more ROS to create more damage, especially to the DNA. An enzyme named poly-ADP-ribose polymerase-1 then comes in to help relocate the damaged DNA. If the enzyme is not present as in many cases of neurodegeneration, a translocation to the nucleus cannot occur, therefore the death caspases are activated, causing apoptosis to be initiated. (Krantic et al., 2005). This is an especially dominant process in motor neurons in the cortex, brain stem, and spinal cord in Amyotrophic Lateral Sclerosis and in the substantia nigra in Parkinson's disease.

Reactive oxygen species cause damage to the mitochondria, which is in the most part, where they are produced. They cause damage to the mtDNA itself to produce a vicious cycle of the mitochondria that is never ending. When ROS start to accumulate, they activate the glial cells, more specifically, the microglia and astrocytes, to cause neuroinflammation and glutamate excitotoxicity. Reactive oxygen species can also cause damage to RNA and DNA of the cells, to cause apoptosis. These molecules with unpaired electrons have detrimental effects on the brain, the neurons, and the central nervous system as a whole, and can not only initiate neurodegeneration, but can also progress it. (Ramalingam & Kim, 2012)

**Metabolic Derangements and Neurodegenerative Disease**

A recent interest in neurodegeneration has been faulty insulin signaling and decreased glucose metabolism in the brain (Frisardi et al., 2010). Research has found a decline in the brain's ability to metabolize glucose, known as hypometabolism, with neurodegeneration. We know that this impaired glucose metabolism is in accordance with the damaged mitochondria. This happens because many of the key metabolic enzymes are impaired, causing metabolism to be altered. Another factor in the efficiency of glucose metabolism is insulin signaling. In neurodegeneration there is a defect in insulin
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

signaling. Sensitivity to insulin is not only important for the maintenance of glucose metabolism, but it is also important for learning and memory skills, and in some cases synapse plasticity (Gasparini et al., 2002). Resistance to insulin causes a deficient metabolism of glucose, which results in less ATP made for the cell (Rasgon & Jarvik, 2004). It also has been proven to be linked to cognitive function, and dementia. Impaired glucose metabolism causes problems with acetylcholine formation and disrupts synaptic transmission causing cognitive dysfunction. One hypothesized way the brain becomes insulin resistant is by the activity of the IR-tyrosine kinase being decreased, bringing about an error in insulin signal transduction (Gasparini et al., 2002). It also becomes resistant to insulin through reactive oxygen species damage (Son et al., 2011). This is the main connection between neurodegeneration and Diabetes Mellitus (diabetes type II).

Insulin has been found to govern the metabolism of two of the main proteins that accumulate in Alzheimer’s disease. These proteins are known as the beta amyloid protein and the tau protein. Tau is a protein that usually binds to microtubules and initiates tubulin polymerization (Frisardi et al., 2011). The tau protein is regulated by phosphorylation through kinases. Consequently, these kinases are down-regulated by insulin and insulin growth factor-1 (IGF-1). Therefore, experimental data has shown that an increase in insulin and IGF-1 comes with a decrease in tau phosphorylation and activation. This means that the tau protein will function normally. However, if the brain is insulin resistant, these processes cannot occur and the tau protein is phosphorylated to cause over-activation. Insulin also regulates the metabolism of the beta amyloid protein in the brain.

Insulin has been shown to help with the clearance of the beta-amyloid precursor protein. With a decrease in insulin sensitivity, comes an increase in the beta-amyloid precursor protein. There is a wide variety of hypotheses on how this works and it is still not clear how this happens (Gasparini et al., 2002). The figure below (Figure 4) shows how insulin resistance initiates protein accumulation in
Alzheimer's disease with other factors, leading to neuron death.

**Figure 4**- (Son et al., 2011).

**Other Diseases Related to Neurodegenerative Diseases**

Like many other diseases, neurodegenerative diseases have other diseases that are closely linked in their etiology and pathogenesis. The first disorder that has a significant relationship with neurodegenerative diseases is Down's syndrome or Trisomy 21 (Kim et al., 2000; Holtzman et al., 1996). There is compelling evidence that people with Down's syndrome have a greater chance of getting Alzheimer's disease, Parkinson's disease, or Huntington's disease. The brain of a person with Down's syndrome has abnormal neurons, with an accumulation of reactive oxygen species in them. This causes apoptosis, inflammation, and all of the damaging effects of reactive oxygen species in the neurons of a person with Down's syndrome. These reactive oxygen species are partly the cause of the decrease in cognition seen in Down's syndrome, and this is one way this disease predisposes a person...
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

to Alzheimer's disease and other neurodegeneration (Busciglio & Yankner, 1995).

There is also a compound called dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (Dyrk1A) that is over-expressed in Down's syndrome brains. Dyrk1A phosphorylates part of the beta amyloid precursor protein, which increases production of the amyloid precursor protein itself. Dyrk1A also helps to phosphorylate tau proteins in Down syndrome brains. Both of these processes help to create abnormal accumulation of these proteins, leading to the pathogenesis of Alzheimer's disease. The plaques that are observed in geriatric Alzheimer's patients are observed in middle aged people with Down's syndrome (McQuillan et al., 2003). Dyrk1A is also related to causing accumulation of other proteins related to other neurodegenerative diseases, including α-synuclein and huntingtin-interacting protein. This increases the likeliness of a person with Down's syndrome to acquire Parkinson’s disease or Huntington’s disease (Park et al., 2009). Many people with Down's syndrome start showing symptoms of Alzheimer's disease and other dementia by middle age (Park et al., 2009; Holtzman et al., 1996).

Another disease strongly associated with neurodegeneration, specifically Alzheimer's disease, is Diabetes Mellitus or diabetes II (Colca & Feinstein, 2012; Beeri et al., 2005). Diabetes Mellitus is characterized by the resistance to insulin in the body, causing metabolism problems, and in many cases obesity (Vellas & Sinclair, 2004). Diabetes Mellitus has recently been shown to cause problems with the central nervous system and cognitive functions, resulting in dementia and neurodegeneration (Gasparini et al., 2002). Diabetes II is the cause of insulin resistance and has been seen to progress protein accumulation in Alzheimer's disease (Michal et al., 2005). Insulin, when normally metabolized in the brain, helps to clear the amyloid beta precursor protein, and helps to down regulate the phosphorylation of the tau protein (Son et al., 2011). Both of these processes are helpful in avoiding the initiation and progression of Alzheimer's disease. However in Diabetes Mellitus, insulin resistance is
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

increased, and these processes do not occur in the brain, increasing the chances of a person with Diabetes type II to get Alzheimer's disease. (Korf et al., 2006)

Neurodegeneration has been specifically linked to both Down's syndrome and Diabetes Mellitus. There have been many hypotheses about how these diseases are connected, and it is still being researched today. Although no breakthrough cures have been found to counteract the trisomy driven changes seen in Down's syndrome, many compounds have been found to help with Diabetes Mellitus. Therefore, the compounds used to help treat Diabetes Mellitus have also been studied for their effects on neurodegeneration, especially on Alzheimer's disease.

Treatment of Neurodegeneration

There have been many proposed mechanisms as to how to slow down, or even stop the process of neurodegeneration. Some have been experimented with, and have been proven ineffective. Others have been effective to stop the symptoms, but not the progression of the disease, and even more are still being studied.

Insulin resistance plays a big part in neurodegeneration, especially in Alzheimer's disease with the formation of plaques. Many researchers have found that compounds which sensitize to insulin can help slow neurodegeneration. These compounds are also used in the treatment of Diabetes Mellitus, as insulin resistance is the main component in this disorder. Thiazolidinediones (TZDs) used to be the most common form of insulin sensitizers. Two of these compounds are rosiglitazone and pioglitazone. These compounds “act as agonists of nuclear receptor peroxisome proliferator-activated receptor-gamma (PPAR-γ)” (Son et al., 2011) to directly active the PPAR-γ (Berger & Moller, 2002). This helps to sensitize the brain to insulin to stop the progression of neurodegeneration and protein accumulation, and to also decrease neuroinflammation. There are also insulin sensitizing hormones such as ghrelin. Ghrelin has been found to decrease the phosphorylation of the tau protein, by sensitizing the brain to
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

insulin. Many types of these compounds are still being researched; however some are being used now to decrease the progression of Alzheimer's disease and neurodegeneration as a whole. (Son et al., 2011). Unfortunately, compounds like rosiglitazone and pioglitazone have been found to have adverse side effects, and this is why studies are still being done to replace them with alternative compounds. (Colca et al., 2013).

There is also another class of insulin sensitizing compounds to help with the treatment of neurodegeneration, however these are aimed at a different process in the cell. Since TZDs have been shown to have damaging effects on the body by directly activating the PPAR-γ, research has been done to find a different way to sensitize the brain and the body to insulin. New TZDs, known as mitochondrial target of thiazolidinediones (mTOTs), with a target protein located on the inner membrane of the mitochondria have become popular, as they work in a way to “change nutrient sensing pathways and modify Wnt signaling” (Colca & Feinstein, 2012). A change in nutrient sensing pathways includes an activation of AMPK, a decrease in mTOR activity, and a decrease in inflammatory kinase activation all which leads to increased insulin activity (Colca et al., 2013). An mTOT compound that is currently being tested for the use on Alzheimer's patients is called MSDC-0160, which should, in addition to sensitizing the brain to insulin, stabilize glucose metabolism as well. (Colca & Feinstein, 2012).

Mitochondrial dysfunction is a major part of neurodegeneration. Therefore the mitochondria have a large role in finding therapeutic means of treating neurodegeneration. The mitochondria serve as a good target for insulin sensitizers and can be a target for other specific types of therapies as well (Reddy & Reddy, 2011). It is known that disease specific proteins and compounds relating to Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS accumulate and associate with the mitochondria, including amyloid β protein, α-synuclein protein, parkin, presenelin, huntingtin, and
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

SOD1. Studies are starting to be done to use this information along with the mitochondria as a therapeutic target to make a compound to treat neurodegeneration. For a specific example, reducing amounts of p53 in the mitochondria protects against the mutant huntingtin protein, treating Huntington's disease. This is just one out of many cases where the mitochondria were used as the specific target for treatment of neurodegeneration (Lin & Beal, 2006). Another way the mitochondria are targeted for treatment is through artificially increasing the amounts of ATP in the mitochondria, which would not only help to increase cellular processes like autophagy, but also “increase synaptic outgrowth and neuronal connectivity.” (Reddy et al., 2011).

Another large branch of targets for treatments of neurodegeneration is the reactive oxygen species. A brain with neurodegeneration has an accumulation of reactive oxygen species, with less antioxidant to defend itself from the harm of ROS. If less reactive oxygen species were found in the brain, there would be less damage to not only the mitochondria, but to the neurons all together. This is why antioxidants have been proposed to be a therapeutic mechanism for neurodegeneration. Mitochondrial targeted antioxidants termed triphenylphosphonium-based antioxidants have been created, because this is where the majority of reactive oxygen species are formed. These are still in research, but they seem to be more effective than just simple vitamin C and E (Reddy et al., 2011), because they are able to cross the blood brain barrier and enter the mitochondria in the neurons. There have also been findings that certain foods and drinks may have antioxidant effects on the brain as well. These include curry spice, fruits, vegetables, and green tea (Calabrese et al., 2006; Mandel et al., 2008). Curry spice contains an antioxidant called curcumin, where fruits and vegetables contain ferulic acid. Both of these antioxidants were seen to have positive effects on the brain. Green tea contains a component called epigallocatechin-3-gallate that has been found to protect the brain from ROS and neuroinflammation (Mandel et al., 2008). Finally the compound melatonin has proven to be a powerful
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

antioxidant against ROS and NO. Melatonin protects mitochondrial DNA from damage by the reactive oxygen species, and allows oxidative phosphorylation to continue undamaged, helping to maintain a good number of ATP (Cardinali et al., 2013).

There are a number of ways researchers have begun to try to treat neurodegeneration. From sensitizing the brain to insulin, to targeting the mitochondria directly, to increasing the defense against reactive oxygen species, numerous aspects surrounding neurodegeneration have been studied. Various compounds are now in trial, and the outlook is positive, however nothing at this point is surely a cure of neurodegeneration. Neurodegenerative diseases are very complicated and as suspected; the cure will be as well.

Conclusion

The incidence of neurodegenerative diseases is rising every year as the elderly population grows. The devastation that occurs from neurodegeneration is due to many different processes happening in the central nervous system. Although each neurodegenerative disease has different profiles of protein accumulation and aggregation, these diseases are thought to have many similarities in pathogenesis.

Mitochondrial dysfunction plays a significant role in the neurodegeneration of the brain. Mitochondrial dysfunction occurs from mtDNA mutations, reactive oxygen species, loss of calcium homeostasis, and protein accumulation in the mitochondria itself. Once reactive oxygen species form, they can cause detrimental effects to our neurons like neuroinflammation, apoptosis, damage to proteasomal function, and damage to DNA and mtDNA. Derangement of the metabolism of reactive oxygen species, protein, and glucose all cause problems in the brain. With a defect in glucose metabolism comes problems in insulin signaling and insulin sensitivity, which brings about specific pathology relating to Alzheimer’s disease. Many of these problems have specific relationships to certain
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

disorders, especially to Down's syndrome and to Diabetes Mellitus.

To treat neurodegenerative diseases, the mitochondria have become a prime target. In many models pathology initiates in the mitochondria, making it a good place to start for therapeutics to cure neurodegeneration. Insulin sensitization is another way that treatment of neurodegeneration could be achieved, as it could restore glucose metabolism and ATP production. Finally antioxidants play a role in the treatment of neurodegeneration, since ROS accumulation is a big part in the neurodegeneration of a human. Neurodegeneration is a very complicated disease, and it will take a lot of time and research to come up with specific treatments to prevent it from occurring.
Acknowledgments

I would like to thank Dr. Robert Eversole for taking the time to be the mentor for this thesis, for editing, and for contributing advice and knowledge. I would like to thank Dr. Jerry Colca for agreeing to be a member of the thesis committee, and for helping to better my understanding in this field of study. I would also like to thank Dr. Charles Ide for taking the time to be a thesis committee member and for contributing his knowledge.

Bibliography

Andersen, J. K. (2004). Oxidative stress in neurodegeneration: Cause or consequence? *Nature Medicine, 10* Suppl 1(7), S18-25. doi:http://dx.doi.org/10.1038/nrn1434


MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION


Everson, R., & Hauptman, J. (2012). From the bench to the bedside: Brain-machine interfaces in spinal cord injury, the blood-brain barrier, and neurodegeneration, using the hippocampus to improve cognition, metabolism, and epilepsy, and understanding axonal death. *Surgical Neurology International, 3*(1), 108. doi:http://dx.doi.org/10.4103/2152-7806.101002

MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION


MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION


Nakamura, T., & Lipton, S. A. (2007). Molecular mechanisms of nitrosative stress-mediated protein misfolding in neurodegenerative diseases.*Cellular and Molecular Life Sciences*,64(13), 1609-
MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION

20. doi:http://dx.doi.org/10.1007/s00018-007-6525-0


MITOCHONDRIAL DYSFUNCTION AND REACTIVE OXYGEN SPECIES IN NEURODEGENERATION


