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Studies on Some Diseases Associated with Mitochondrial Disorder

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Abstract: *This work was aimed at studying some diseases associated with a mitochondrial disorder. Mitochondria are tiny structures inside almost every cell in the body; all the way from the skin to the organs inside the body. Their main job is to use the food and oxygen that enter the cells to make energy. Almost all of the energy the body needs for daily life and growth comes from mitochondria are ubiquitous subcellular organelles that play essential roles in energy production, metabolism, and signal transduction. The energy generated in this oxidative phosphorylation process is utilized for the synthesis of adenosine triphosphate (ATP), Mitochondria are also involved in programmed cell death or apoptosis. The term "Mitochondrial disease" refers to a group of disorders; each of these conditions involves a problem with mitochondria which can arise from two sources: mutations of DNA in mitochondria, or mutations of DNA in nuclear genes. Mitochondrial DNA has a mutation rate of about ten times that of nuclear DNA. Symptoms include: Developmental delay or regression in development, seizures, migraine headaches or strokes, muscle weakness (maybe on and off), poor muscle tone (hypotonia), poor balance (ataxia), painful muscle cramps, unable to keep up with peers (low endurance), chronic fatigue, stomach problems (vomiting, constipation, pain), temperature problems from too little or too much sweating, breathing problems, eyes are not straight (strabismus), decreased eye movement (ophthalmoplegia), loss of vision or blindness, droopy eyelids (ptosis), loss of hearing or deafness, heart, liver or kidney disease at a young age, parts of the body are shaky (tremors) Medications are used to treat certain symptoms such as Seizures can be controlled with medications called anticonvulsants, Muscle cramping and stiffness may be relieved with medications called muscle relaxants, Spasticity (tight or rigid muscles that constantly contract). Creating monohydrate, Vitamin C, Vitamin E, Alpha lipoid acid, Co-enzyme Q10, Riboflavin, Thiamine, L-carnitine are some of the drugs of choice.*

Key words: *Mitochondria, DNA, Disease & Symptoms*

INTRODUCTION

Mitochondria are tiny structures inside almost every cell in the body; all the way from the skin to the organs inside the body. Their main job is to use the food and oxygen that enter the cells to make energy. Almost all of the energy your body needs for daily life and growth comes from

mitochondria are ubiquitous subcellular organelles that play essential roles in energy production, metabolism, and signal transduction (Martinou and Youle, 2011) Multimeric protein complexes organized within the inner membrane of the mitochondrion catalyze the reactions in the citric acid cycle and transport of electrons, resulting in the formation of a proton gradient. The energy generated in this oxidative phosphorylation process is utilized for the synthesis of adenosine triphosphate (ATP), which drives a multitude of necessitous reactions within all cells, especially those with high energy requirements such as neurons and myocytes (Cheng and Ristow, 2013) Mitochondria are also involved in programmed cell death, or apoptosis; whereby upon detection of a stress signal, they will release cytochrome c into the cytosol which triggers downstream caspases to initiate apoptosis (Renault & ChipuK (2014).

MORPHOLOGY IN RELATION TO FUNCTION

As evidence of the impact of mitochondrial structure on function (Heath & Shore, 2006), some have shown that enhanced network branching induced by up-regulating mitochondrial fusion (Ong *et al.* 2010) or else down-regulating fission (Ong et al. 2010) can decrease or prevent apoptotic signalling. Inhibiting mitochondrial fission also prevents fission-induced ROS release in hyperglycaemic conditions (Yu et al. 2006). The opposite also appears to occur: enhanced network fragmentation by upregulating mitochondrial fission (Frank *et al.* 2001; Ong et al. 2010) or downregulating mitochondrial fusion (Lee et al. 2004) can promote pro-apoptotic signalling in live cells, although this causal link has not always been observed (Youle & Karbowski, 2005). Further to this, promoting mitochondrial fission and network fragmentation has been associated with reduced respiratory capacity and increased ROS production (Yuet al. 2008). In addition, the major protein involved in mitochondrial fusion – mitofusin 2 – influences expression of oxidative phosphorylation genes (Pich *et al.* 2005), indicating overlap at the genetic level between regulatory pathways for mitochondrial morphology and metabolism (Zorzano *et al.,* 2010). Mitochondrial membrane potential is also closely associated with reversible changes in mitochondrial morphology (Guillery *et al.* 2008), and additional findings demonstrate an intricate relationship between mitochondrial dynamics, structure and function (McBride & Soubannier, 2010).

MORPHOLOGY AND ORGANELLE INTERACTIONS

The classic picture of cellular mitochondria based on low-resolution electron micrographs is of a set of relatively small bean shaped particles scattered around the cytosol. However, our understanding of the morphology of the organelle has changed with the advent of higher resolution electron microscopes and cryopreservation of samples. Foremost, mitochondria are now known to be highly dynamic and can be punctate as previously proposed, but can also be organized as a continuum or reticulum under some cell conditions. Further, the organelle moves within the cell in the punctate state or as a reticular unit to provide foci of energy production such as at the nucleus during cell division, or to synapses in neuronal cells at times of high information transfer.

INTERNAL STRUCTURE

A typical low-resolution electron micrograph of bovine heart mitochondria is shown below. Such images led to a model in which there was a distinct outer membrane and a convoluted inner membrane surrounding the matrix space. These convolutions were called cristae. The space between the inner and outer membranes was called the intracristal space. Improved electron microscopy techniques have provided a more complex picture.

ORGANIZATION OF MITOCHONDRIAL GENOME

A unique feature of mitochondria is that they contain their own mitochondrial DNA (mtDNA). This genome is a relic of their free living bacterial origins before they were engulfed by ancient eukaryotes and co-opted for aerobic respiration. Compared to the nuclear genome, replication of the mitochondrial genome is not tightly controlled and may occur at any stage of the cell cycle, instead of being confined to mitosis and meiosis (Ristow, 2013) This results in varying mtDNA copy numbers per cell(Pohjoismäki & Goffart, 2011) . Most human cells contain at least 1,000 mtDNA molecules distributed among hundreds of mitochondria, except for mature human oocytes, which have more than 100,000 mtDNA copies. (Veltri KL & Espiritu1990) . The human mitochondrial genome is composed of double-stranded circular DNA approximately 16.6 kbp in size and contains 37 genes. These genes encode 2 rRNA, 22 tRNA, and 13 polypeptides that are subunits of the OXPHOS system (8). All remaining components required by the mitochondria, such as DNA polymerases and other subunits of OXPHOS, are encoded by the nuclear genome. Except for a small regulatory region called the displacement loop (D-loop), the entire mitochondrial genome is comprised of coding sequences (Nussbaum et al., 2007). This characteristic, compounded with the greater potential for oxidative damage and lack of any internal DNA repair mechanisms, makes mtDNA about 10 times more likely to acquire mutations compared with nuclear DNA (Spelbrink, 2010).

What are the signs and symptoms?

Every cell in the body, except red blood cells, contains hundreds to thousands of mitochondria working to make energy. The mitochondria in some areas of the body may be working properly, but not in other areas. This can cause a wide variety of symptoms.

There is no one identifying sign or feature of mitochondrial disease. Symptoms can vary and range from mild to severe, even among affected family members. In mild cases, young people may learn to cope and adapt to the amount of energy they have and don't realize they have symptoms, or adults may comment that they were very healthy as a child, but not really athletic.

People with Mitochondrial disease often have one of more of these symptoms: Developmental delay or regression in development, seizures, migraine headaches or strokes, muscle weakness (may be on and off), poor muscle tone (hypotonia), poor balance (ataxia), painful muscle cramps, unable to keep up with peers (low endurance), chronic fatigue, stomach problems

(vomiting, constipation, pain), temperature problems from too little or too much sweating, breathing problems, eyes are not straight (strabismus), decreased eye movement (ophthalmoplegia), loss of vision or blindness, droopy eye lids (ptosis), loss of hearing or deafness, heart, liver or kidney disease at a young age, parts of the body are shaky (tremors) (Hamilton, 2010)

MITOCHONDRIAL DISEASES

The term "Mitochondrial disease" refers to a group of disorders; each of these conditions involves a problem with mitochondria

HOW IT HAPPENS

Mitochondrial disorders can arise from two sources: mutations of DNA in mitochondria, or mutations of DNA in nuclear genes. Mitochondrial DNA has a mutation rate of about ten times that of nuclear DNA(Yakes and Van Houten 1997) This may be because there are so many more mitochondria per cell compared with two pairs of nDNA genes per cell, and also that the system of replication of mitochondria is prone to errors due to less efficient systems for DNA repair(Linnane et al.,1989)

Mitochondria and Neurodegeneration

It has long been thought that mitochondria play a critical role in a variety of diseases characterized by neuro-degeneration. Early on the focus was on oxidative stress and the effect this had on energy production. More recently emphasis has shifted to disease-causing alterations in mitochondrial trafficking and/or removal of defective organelle by mitophagy (Hamilton Health Science, 2010)

Role of Mitochondria in Parkinson's diseases. Although as of now there is no definitive evidence in any of the diseases below. The proposal that mitochondrial dysfunction played a role in Parkinsons disease originated with the observation that the Complex I inhibitors rotenone and MTTP caused Parkinsonian symptoms. More recent work has identified Complex I protein changes in patients with the disease. Proteomic studies showed that complex I of brains from Parkinsons patients had an average decrease of 34% in the 8 kDa subunit, and contained 47% more protein carbonyls in catalytic subunits coded for by mitochondrial and nuclear genomes. Further, NADH-driven electron transfer rates through complex I inversely correlate with complex I protein subunit modifications. Similar patterns were observed when the mitochondria from brains of control subjects were incubated with NADH in the presence of rotenone, but not with exogenous oxidant, indicating that the oxidative damage is induced from within the complex and not by exogenous free radicals. The damage caused by Complex I dysfunction and consequent superoxide production is broader than just in this complex, and is found in DNA, lipids and proteins of PD brains, particularly in the substancia nigra which has low concentrations of anti-oxidant proteins. Oxidative damage is also seen in peripheral tissues.

Importantly, these broad oxidative effects are observed in animals treated with rotenone, confirming that the initial free radical generator is Complex I (Christoffels et al., 2015)

Mitochondria and Alzheimers Disease (AD).

As in PD, membrane-associated oxidative stress, increased free radical production, and perturbed Ca2+ homeostasis have been observed. Increased mitochondrial permeability and cyt c release, which is promoted by Aβ oligomerization and polymerization, is thought to trigger the opening of MPTP leading to apoptosis. Different from PD there is evidence of reduced cytochrome c oxidase activity. This is at least in part due to oxidative damage of mtDNA that is beyond that seen in normal age controls. Complex I down regulation is also seen in AD brains. As in PD, the primary insult leading to AD is not known. Most likely this is a heterogeneous disease, with altered mitochondrial function leading to reduced ATP production, increased free radical production, and increased apoptosis (Reddy & Beal2008)

Mitochondria and Huntingtons Disease

Huntingtons disease is linked to the presence of an elongated polyglutamine (polyQ) stretch in the huntingtin protein (Htt). This mutation in Htt correlates with neuronal dysfunction in the striatum and cerebral cortex and eventually leads to neuronal cell death. How this happens remains unclear but like PD and AD focus is now on anomalous mitochondrial dynamics, and trafficking along with disrupted mitophagy. In addition, deficiency in oxidative metabolism and defects in mitochondrial Ca2+ handling are considered essential contributing factors to neuronal dysfunction in HD (Guedes *et al*., 2016)

Amiotrophic Lateral Sclerosis

Amiotrophic lateral sclerosis or ALS has been shown to involve the misfolding of the predominantly cytosolic antioxidant protein superoxide dismutase (SOD1). Mitochondria also contain SOD1 as well as a second form of this enzyme SOD2, which is not affected by the disease. Wild type SOD1, and a copper chaperone for SOD1 (CCS), are localized to the intermembrane space (IMS) in normal mitochondria. It has been proposed that the nascent SOD1 polypeptide with no metal ion bound can efficiently enter mitochondria and that the maturation of SOD1 including metal ion binding and intra-molecular disulfide bond formation inside mitochondria and the subsequent retention in IMS involve the SOD1-CCS interaction. The ALS-related mutant SOD1 proteins have also been found in the IMS, but also in the matrix and outer membrane of mitochondria. Once associated with mitochondria, the mutant SOD1 is seen to cause impaired respiratory complexes, disrupted redox homeostasis, and decreased ATP production. However, the primary effect could be altered mitochondrial cell transport As in Parkinsons disease, the reason that mitochondrial dysfunction is observed predominantly in neurons may relate to altered mitochondrial cell transport in these extended cells. Thus it has been shown that primary neurons isolated from G93A SOD1 transgenic mice and cortical neurons transfected with G93A SOD1, have reduced antegrade mitochondrial transport.

CURRENT TREATMENT OPTIONS

Whether caused by mutations in mitochondrial genes or in nuclear genes related to mitochondrial function, mitochondrial disorders are relatively rare in the population. A study in 2008 found that one in 200 children is born each year with a disease-causing mitochondrial DNA mutation, but in most cases these are due to a very low mutation load these cause only mild forms of mitochondrial disorders or are asymptomatic. However, these pathogenic mutations could nonetheless be passed on to future children at more significant levels (Elliott et al 2008). It was also previously thought that least one in 8,500 of the population carried mitochondrial DNA mutation with a disease-causing mutation load(Schaefer et al., 2004) It has been calculated that at least 3,500 women in the UK, many of whom are of childbearing age, carry a potentially problematic level of mtDNA mutation, but this may be an underestimate(Brown et al., 2006)

It is difficult to be precise as to how many people are affected by mitochondrial DNA disorders, as there is thought to be a high rate of under-diagnosis and misdiagnosis due to the wide range and varying severity of the symptoms experienced. It can also be hard to establish whether a mitochondrial disorder has been caused by problems in nuclear genes or mitochondrial genes. New mitochondrial disorders are also still being identified. An estimated figure for the total prevalence of people affected by mitochondrial DNA disorders and mitochondrial disorders caused by nuclear genes is 1 in 5,000(Schaefer et al., 2004)

MEDICATIONS AND SUPPLEMENTS

Medications are used to treat certain symptoms such as:

Seizures can be controlled with medications called anti-convulsants

Muscle cramping and stiffness may be relieved with medications called muscle relaxants

Spasticity (tight or rigid muscles that constantly contract) can be eased with medications or injections of Botox

Recent research has shown that several vitamin supplements can help relieve symptoms and improve function: Creatine monohydrate, Vitamin C, Vitamin E, Alpha lipoic acid, Co-enzyme Q10, Riboflavin, Rhiamine, L-carnitine, L-arginine

CONCLUTION:

In conclusion, it realised that mitochondrial infection occurs within the population. A clinical and diagnostic method exists but the most reliable and significant method of treatment has a low success rate. However, with recent advancements in therapeutic cloning involving genetic transfer, it is obvious that absolute treatment could soon be achieved

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