MitoInsights

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Lay Summary: Antioxidants and Creatine to Support Mitochondrial Function in LHON Cells

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What's this research about?

Leber Hereditary Optic Neuropathy (LHON) is a rare mitochondrial disease that causes sudden, painless loss of central vision. Most cases are caused by mutations in mitochondrial DNA that affect Complex I, one of the key components of the cell's energy-producing machinery. Additionally, Complex I is also the site of mitochondrial free radical production. Free radicals are unstable molecules produced during normal cell processes, including energy production in mitochondria. When too many free radicals build up, they can damage cells and contribute to oxidative stress.

In a dysfunctional mitochondrion, such as in the example of an LHON-affected cell, these free radicals far exceed levels the cell can handle; they build up and start damaging cellular components within the cell, including DNA, proteins, membranes and other mitochondria within the cell. Idebenone is a small molecule that helps LHON-affected mitochondria produce less free radicals. However, while idebenone has helped thousands of patients worldwide, and currently is the only approved disease-specific treatment for LHON in several countries, not everyone responds to it, and researchers are actively searching for additional therapies that may help a broader range of patients.

In this study, researchers from McMaster University investigated whether a combination of readily available supplements, including creatine, CoQ10, alpha-lipoic acid, and vitamin E, could improve mitochondrial function in cells taken from people with LHON. They called this combination treatment ACT (Antioxidant and Creatine Treatment). The team wanted to understand both the common biological problems shared across different LHON mutations and whether this supplement combination could help address them.

Why is this important?

Although LHON is caused by mutations in mitochondrial DNA, not all patients experience the disease in the same way. Different mutations can lead to different levels of disease severity, and even people with the same mutation may have different outcomes. This makes it challenging to develop treatments that work for everyone.

The only approved treatment, idebenone, also has limitations. Recent research has shown that its effectiveness depends partly on the presence of a protein called NQO1, which helps activate the drug. Some people naturally have genetic variants that lead to low levels of this protein, meaning idebenone may not work as well for them, and can actually increase oxidative stress (a state when the body produces more free radicals than cells can manage and keep under control). Oxidative stress is an important factor in the development and progression of LHON. This highlights the need for additional treatment options that could benefit people regardless of their genetic background.

Finding therapies that can reduce oxidative stress from free radicals, improve energy production, and support mitochondrial health could potentially benefit many people living with LHON and may provide insights that extend to other mitochondrial diseases as well.

How did they study this?

The researchers collected skin biopsies from people with LHON carrying three different mitochondrial DNA mutations. From these samples, they grew fibroblasts, cells commonly used in laboratory research to study mitochondrial function. These cells were compared with fibroblasts from healthy individuals of similar age and sex.

First, the team carefully examined the mitochondrial health of the LHON cells. They measured how well the mitochondria were working, including energy production, levels of reactive oxygen species- oxygen containing molecules naturally produced by cells that can contribute to cell damage when too many build up. The researchers also looked at how efficiently cells remove and recycle damaged proteins and mitochondria through a process called autophagy.

Next, they treated the cells with either idebenone or the ACT supplement combination. The ACT formula (containing creatine, CoQ10, alpha-lipoic acid, and vitamin E) was based upon earlier work by Dr. Tarnopolsky's group showing that this combination lowered oxidative stress and lactate in patients with MELAS, CPEO and LHON in a clinical trial. The researchers then evaluated how the treatments affected mitochondrial function, resistance to cellular stress, oxidative damage, and autophagy.

What did they find?

The researchers discovered that despite differences between mutations, LHON cells shared several common mitochondrial problems. Compared to healthy cells, they produced higher levels of reactive oxygen species, had impaired energy production, and showed abnormalities in autophagy- the cells clean-up and recycling process. Specifically, LHON cells showed signs of a stalled process of autophagy; although the cells could still package damaged proteins and mitochondria into cellular "garbage bins," a slower removal process led to a greater build-up of waste.

When the cells were treated with the ACT combination, several positive changes occurred. The treatment reduced oxidative stress, improved mitochondrial respiration (how mitochondria convert nutrients and oxygen into cellular energy), increased the cells' ability to withstand environmental stressors, and helped "speed up" autophagy, normalizing it to levels seen in healthy cells. In many cases, the improvements were equal to those seen with idebenone. For some outcomes, the ACT supplement combination performed even better.

One particularly important finding was that ACT worked independently of NQO1 protein levels. While idebenone's effectiveness appeared closely linked to the amount of NQO1 protein present in the cells, the benefits of ACT did not depend on NQO1. This suggests the supplement combination could potentially be effective in individuals who may not respond optimally to idebenone due to genetic variants in the *NQO1* gene.

The researchers also found that repeated ACT treatment reduced markers of oxidative stress, increased the energy producing units of the mitochondria and overall improved the efficiency of energy production, by promoting the removal of damaged mitochondria, and helping normalize the cellular systems that maintain healthy mitochondria, such as autophagy.

What does this mean for mitochondrial disease research?

This study provides evidence that several mitochondrial problems seen in LHON, including oxidative stress, impaired energy production, and disrupted mitochondrial quality control, may be addressed through a multi-ingredient supplement approach.

Importantly, the research also highlights that mitochondrial diseases involve more than simply reduced energy production. The investigators found that defects in autophagy appear to play an important role in LHON. Understanding these pathways may open new directions for future therapies.

Because the treatment improved mitochondrial function across multiple LHON mutations and did not rely on NQO1 protein activity, the findings suggest that broader treatment strategies targeting mitochondrial health may have value in genetically diverse patient populations. Although these experiments were conducted in patient-derived cells in the laboratory, the same combination of supplements lowered oxidative stress and lactate in patients with MELAS, CPEO and LHON in a randomized human clinical trial and have been available in Ontario for patients with primary mitochondrial disease for over 20 years though the Inherited Metabolic Disease program.

In simple terms, what is this study about?

Researchers took cells from people with LHON and tested whether a combination of common mitochondrial-supporting supplements could improve how those cells functioned. They found that the treatment reduced harmful oxidative stress, helped the cells produce energy more effectively, and improved some of the cellular processes that keep mitochondria healthy. In many cases, the results were similar, or superior, to those seen with idebenone, the current approved treatment for LHON, but without Idebenone's limited applicability to all patients.

Why does this matter to the mito community?

Many people living with mitochondrial disease are interested in nutritional and supplement-based approaches that may support mitochondrial health. In this study, researchers from McMaster University investigated whether a laboratory-prepared combination of readily available supplements, including creatine, CoQ10, alpha-lipoic acid, and vitamin E, could improve mitochondrial function in cells taken from people with LHON.

The findings are especially encouraging because the treatment appeared to work across multiple LHON mutations and did not depend on the NQO1 protein levels, a factor that can influence response to idebenone. For families affected by LHON, this research offers another avenue worth exploring in future clinical studies and reinforces the importance of targeting mitochondrial health from multiple angles.

Perhaps most importantly, this study reminds us that even when a disease is caused by a genetic mutation, researchers can still look for ways to strengthen the cell's resilience, improve mitochondrial function, and help cells better cope with stress. Those approaches may ultimately complement future gene-based therapies and contribute to better outcomes for people living with mitochondrial disease.

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