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REPORT

Mitochondria and the Evolution of Human Longevity

One of the hottest areas in medical research today explores the impact of the mitochondria on human houses found in every cell. Mitochondria were once seen as the place where nutrients are converted to energy—and nothing more. Now scientists are discovering that the mitochondria are central to the evolution of human longevity.

A fascinating Harvard Medical School study was recently published in the *Journal of Molecular Evolution*.[1] By comparing the mitochondrial genome of various primates, the scientists found that our mitochondria have evolved over time in a way that has allowed humans to lead longer, healthier lives without the scourge of neurodegenerative disease. With the discovery of this critical link to both human longevity and evolution, new emphasis should be placed on proven ways to support and enhance mitochondrial function.

THE MITOCHONDRIAL THEORY OF AGING

Scattered throughout the jelly-like cytoplasm within our cells, the mitochondria range in number from hundreds to thousands per cell. They crank out energy in the form of adenosine triphosphate (ATP), a molecule that we cannot live without. But they do so at a price. According to the mitochondrial theory of aging, free electrons are generated as a byproduct of aerobic respiration (the chain of ATP-producing chemical reactions that occur within the mitochondria). These electrons convert oxygen to a highly reactive form capable of damaging proteins and lipids and wreaking havoc with DNA over time. Progressive respiratory chain dysfunction ensues. Damage accumulates slowly, eventually leading to the degenerative changes associated with aging.[2-4]

As a result, preserving youthful mitochondrial function is of paramount importance to prolonging life span. The good news is that modern science is rapidly discovering an arsenal of nutrients capable of slowing or reversing many of the degenerative changes constantly occurring within our mitochondria. Nutritional supplements such as acetyl-L-carnitine, R-lipoic acid, and coenzyme Q10 have been shown to improve mitochondrial function, while carnosine prevents age-related damage in cells due to glycation (the binding of sugars and proteins in the body). Still other nutrients, such as benfotiamine, Rhodiola rosea, and wheat sprouts, work in various ways to prevent age-associated changes in mitochondrial structure and energy production.

MORE POTENT FORMS OF CARNITINE

Acetyl-L-carnitine and acetyl-L-carnitine arginate are two important nutrients for supporting mitochondrial health and longevity. Acetyl-L-carnitines boost the conversion of fats into energy in the mitochondria, helping to ensure that a plentiful energy supply is available for biochemical processes throughout the body. Because the brain requires abundant energy, these nutrients are especially crucial for peak brain energy and function.

Beyond their ability to neutralize damaging free radicals, acetyl-L-carnitines have been shown to improve various brain health parameters. As one researcher noted recently, “esters such as acetyl-L-carnitine possess unique neuroprotective, neuromodulatory, and neurotrophic properties which may play an important role in counteracting various disease processes.”[5]

For instance, animal research shows that acetyl-L-carnitine reverses age-related decline in the number of receptors present on the surface of nerve cells in the brain. Studies of Alzheimer’s patients have reported improvements in memory compared to patients receiving placebo.[6] Other studies have investigated the effectiveness of adding acetyl-L-carnitine to standard pharmaceutical treatments for Alzheimer’s disease. In a recent Italian study, Alzheimer’s patients in the early phases of the disease took 2 grams of acetyl-L-carnitine daily for three months. Response rates, as determined by a variety of functional and behavioral parameters, improved from 38% with standard acetylcholinesterase inhibitor drugs (such as Aricept®) alone to 50% with the addition of acetyl-L-carnitine.[7] Another placebo-controlled, double-blind study conducted at Stanford University concluded, “Acetyl-L-carnitine slows the progression of Alzheimer’s disease in younger subjects.”[8]

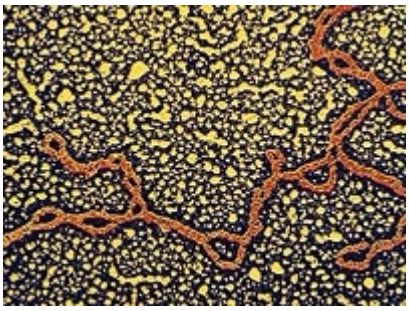
More recently, researchers at Imperial College University in London conducted a statistical meta-analysis of published studies that had examined the effects of acetyl-L-carnitine supplementation versus placebo for the treatment of symptoms of Alzheimer's disease and its precursor condition, mild cognitive impairment. The analysis considered only double-blind, placebo-controlled studies—the scientific "gold standard"—of at least three months' duration. Doses ranged from 1.5 to 3 grams of acetyl-L-carnitine per day. "Meta-analysis showed a significant advantage for [acetyl-L-carnitine] compared to placebo," the researchers concluded. Beneficial effects were noted in both clinical assessments and psychometric tests, and the improvements increased over time. The researchers also noted that acetyl-L-carnitine was well tolerated in all studies.[9]

Acetyl-L-carnitine's benefits are not limited to Alzheimer's patients, however. Aging rats fed acetyl-L-carnitine experienced significant improvements in age-associated changes in brain lipid composition.[10] Other animal studies found that acetyl-L-carnitine supplementation led to remarkable increases in physical activity among aging rats[11,12] as well as improvements in memory,[13] reversal of age-associated hearing loss,[14] and improvements in age-associated glycation of eye lens proteins.[15]

In a cleverly designed study, researchers at the National Center for Toxicological Research recently showed that supplementation with acetyl-L-carnitine's precursor, L-carnitine, prevents experimentally induced mitochondrial dysfunction in laboratory animals.[16] Japanese researchers meanwhile discovered that acetyl-L-carnitine uptake is significantly lower in the brains of patients with chronic fatigue syndrome. The scientists speculated that acetyl-L-carnitine plays an important role in the biosynthesis of neurotransmitters, and that this pathway may be reduced in chronic fatigue patients.[17] Acetyl-L-carnitine supplementation has also been found to alleviate depression among the elderly.[18]

Acetyl-L-carnitine arginate has several valuable properties. The attachment of an arginine molecule to acetyl-L-carnitine gives this compound a number of additional benefits for the aging brain. Acetyl-L-carnitine arginate appears to mimic the effects of a protein called nerve growth factor that supports the survival of neurons in areas of the brain associated with emotion, such as the hippocampus, and in the forebrain, which is associated with cognition, emotion, and important body functions.

As laboratory rats age, they experience a significant loss of neurons and neuronal activity in these areas. These losses are associated with the degeneration of various physiological functions, and are usually accompanied by deteriorating performance on memory tests. One of the possible causes for this degeneration is a reduction in supporting factors such as nerve growth factor. Since acetyl-L-carnitine has been shown to reverse some of these deficits, Italian researchers reasoned that acetyl-L-carnitine arginate might also improve brain function among aging animals.



Electron micrograph of mitochondrial DNA (red).

To test this hypothesis, they added acetyl-L-carnitine arginate to rat brain cells growing in tissue culture without any growth-supporting factors. The brain cells sprouted new connections—tendrils of axons and dendrites—known as neurites. The researchers concluded that acetyl-L-carnitine arginate stimulated this remarkable growth by acting directly on receptors for nerve growth factor located on the surface of nerve cells.[19] This groundbreaking research was later expanded on by researchers at the University of Texas, who experimented on tissue cultures derived from human brain cortex.[20] The discovery that acetyl-L-carnitine arginate stimulates new neurite outgrowth suggests an exciting potential treatment for diseases involving neuronal degeneration, such as Alzheimer's and Parkinson's.

Yet another research team demonstrated that acetyl-L-carnitine protects brain cells from the toxic effects of amyloid beta, the peptide that is believed to trigger cell death when it aggregates in the brains of Alzheimer's patients. Using brain cells in culture, the scientists demonstrated that acetyl-L-carnitine arginate "was able to rescue neurons from [amyloid beta]-induced neurotoxicity."[21]

R-LIPOIC ACID FIGHTS FREE RADICALS

Lipoic acid and acetyl-L-carnitine are the "dynamic duo" of anti-aging nutrients. Like acetyl-L-carnitine, lipoic acid is a natural mitochondrial metabolite, participating in energy-producing reactions in the mitochondria. A potent antioxidant, lipoic acid also helps protect against the free radicals generated during mitochondrial energy production. The "R-" form of lipoic acid is the biologically active form,[22] and numerous studies have paired it with acetyl-L-carnitine to determine the synergistic effects of these two compounds on mitochondrial function. The benefits noted in these studies include improvements in memory, positive changes in age-related hearing loss, and decreased oxidative damage. Furthermore, lipoic helps protect mitochondria against age-associated deterioration in structure that can interfere with optimal function.[12,13,23]

Like acetyl-L-carnitine, R-lipoic acid readily crosses the blood-brain barrier, enabling it to benefit neurons and body cells alike. Although it penetrates cell and mitochondrial membranes, it also benefits the extracellular matrix after conversion in the body to

a still stronger antioxidant, R-dihydro-lipoic acid. This multitasking molecule possesses the rare ability to function as an antioxidant in both water- and fat-soluble tissues,[24] and it is considered an especially potent protector of brain function.

While R-lipoic acid is a potent antioxidant in its own right, it also helps to regenerate the antioxidant capacity of other important antioxidants, such as vitamins C and E, when they are "spent."[25] Additionally, it boosts levels of glutathione, another essential antioxidant. Glutathione is universally recognized as crucial to overall health and immunity, but oral supplementation with glutathione offers limited benefit since it is degraded in the gastrointestinal tract. R-lipoic acid, on the other hand, is readily absorbed and disseminated throughout the body. Optimal levels of these crucial antioxidants are necessary to maintain youthful structure and function of the body's mitochondria, and may be associated with increased longevity.

CARNOSINE HELPS RETARD GLYCATION

Conquering aging requires a multi-pronged science-based strategy. In addition to enhancing our mitochondrial health, defending against glycation can make a significant difference in how we age. Glycation has been shown to reduce the functionality and efficiency of mitochondrial proteins, which in turn promotes cellular death (apoptosis).[26,27] Carnosine is an invaluable weapon in fighting glycation. This dipeptide (two linked amino acids) occurs naturally in our cells and is a potent antioxidant and free radical scavenger. Glycation occurs when proteins or DNA molecules throughout the body bond chemically with sugar molecules. Eventually the sugars are further modified to form advanced glycation end products (AGEs). AGEs are resistant to the body's routine efforts to remove damaged proteins. Ultimately, AGEs cross-link with adjacent proteins, rendering tissue increasingly stiff and inflexible.[28]

This gradual process clearly reveals itself in the mirror as we age. The collagen and elastin in the skin lose their suppleness, causing wrinkles to develop, among other changes. But AGE damage is more than skin deep, as its effects within the body are even more serious. Glycation reduces protein flexibility and functionality. It is the culprit behind cataracts, and plays a role in numerous other degenerative processes such as arthritis and atherosclerosis.[29,30]

Even more serious, AGEs trigger inflammatory reactions throughout the body. In the brain, they have been shown to prompt certain cells to pump out free radicals and immune system factors—such as cytokines and adhesion molecules—that ultimately are toxic to neurons. Many scientists believe that AGEs play a key role in the development of cognitive decline and Alzheimer's disease. AGEs are thought to oxidize brain cell proteins known as tau proteins, which when altered may contribute to neurofibrillary tangles that are associated with Alzheimer's.[31]

Fortunately, there is a way to put the brakes on all this glycation damage. Although skeletal muscle levels of carnosine drop by 63% from age 10 to age 70,[32] it is possible to augment falling supplies with oral supplementation. Doing so slows down or even reverses some of glycation's effects.[33-35] Carnosine also scavenges free radicals, while inactivating reactive chemicals such as aldehydes and lipid peroxidation products.

REPORT

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COENZYME Q10 BOOSTS MITOCHONDRIAL ENERGY

Coenzyme Q10 is one of the most important nutrients for the heart and brain. Since it was first introduced it to the United States in 1983, there has been an explosion of research into its many benefits. We now know that the ability of cells to utilize energy substrates declines precipitously without adequate supplies of CoQ10. And because 95% of cellular energy is produced within the mitochondria, it is clear that CoQ10's ability to help restore mitochondrial function has a profound impact on one's overall health.[36]

A study published in the *Proceedings of the National Academy of Sciences* provides some fascinating insight into the many benefits of this nutrient.[37] After two months of CoQ10 supplementation, mitochondrial energy expenditure in the brains of rats increased by 29% compared to non-supplemented controls. The equivalent human dose to achieve these results is 100-200 mg per day. CoQ10 administration to middle-aged and old rats raised CoQ10 levels by 10-40% in the cerebral cortex region of the brain. This increase was sufficient to restore CoQ10 levels to those seen in young animals. Numerous other studies have confirmed CoQ10's benefits for the brain and cardiovascular system.

BENFOTIAMINE, THIAMINE SUPPORT HEALTHY METABOLISM

One of the most deleterious effects of so-called "normal" aging is rising glucose levels in the body. Failure to control this excess sugar can lead to life-threatening diseases such as metabolic syndrome, diabetes, and cardiovascular disease. Although there are many problems associated with hyperglycemia, they all stem from the root problem of glucose flooding into cells and overwhelming their metabolic machinery. High glucose levels are responsible for increased mitochondrial free radical production and other complications.[38] One of the body's proteins, an enzyme called transketolase, is critical in the metabolism of sugars. But to do its job, transketolase, like many enzymes, requires a co-factor. In this case, it needs assistance from thiamine. Unfortunately, thiamine is water soluble, which makes it less available to the interior of the cell.

Benfotiamine is a slightly altered form of vitamin B1 (thiamine). This alteration renders it fat soluble, allowing it to enter areas of the body where water-soluble thiamine cannot penetrate. Used for more than a decade in Germany, benfotiamine is considerably more available to the cells than thiamine. A landmark study, published recently in the medical journal *Nature Medicine*, found that benfotiamine increases transketolase activity in cell cultures by an astounding 300%. By comparison, thiamine added to cell cultures raises transketolase activity a mere 20%. Benfotiamine's robust activation of transketolase was sufficient to block three of the four major metabolic pathways leading to blood vessel damage.[39]

Additionally, benfotiamine blocked activation of the pro-inflammatory transcription factor, nuclear factor-kappa beta (NF-kB).39 NF-kB has been implicated in inflammation, tumor formation, and the age-related disorder macular degeneration, as well as retinal disease in diabetics.[40] It regulates both cell proliferation and cell "suicide." Blocking NF-kB may also improve the prognosis of arthritis patients.[41] All of these findings suggest still more benefits of benfotiamine therapy in the future.

RHODIOLA BOOSTS MITOCHONDRIAL ENERGY

One of the best herbs for enhancing mitochondrial energy production is Rhodiola rosea. Also known as golden root or Arctic root, rhodiola has been used in traditional medicine for centuries. It has been studied extensively by Russian scientists, who have dubbed it an adaptogen. This term refers to the herb's ability to increase resistance to numerous chemical, physical, and biological stressors, including strenuous exertion, mental strain, and toxic chemicals.[42]

A recent study in rats that were trained to exhaustion found that rhodiola significantly boosted the synthesis and resynthesis of ATP in the mitochondria, which enabled the rats to swim for 24% longer.[43] Rhodiola also reduces fatigue under stressful conditions and exerts an anti-inflammatory effect.[44,45] Richard Brown, MD, assistant professor of clinical psychiatry at Columbia University and author of *The Rhodiola Revolution*, recommends it as an energy booster and treatment for depression, chronic fatigue, and anxiety.[46]

In a randomized, double-blind, placebo-controlled trial with medical students, Russian researchers showed that rhodiola extract improves the capacity to perform mentally demanding tasks under conditions of extreme stress and fatigue.[44] A similarly controlled trial conducted on students during a stressful examination period found that objective and subjective measures of physical and mental performance were significantly superior among subjects who took rhodiola extract compared to placebo.[47] It is believed that rhodiola's beneficial properties stem in part from its ability to influence the activities and levels of brain chemicals such as serotonin and norepinephrine, as well as natural "feel good" opioids such as beta-endorphins.[48]

LUTEOLIN: MITOCHONDRIAL AND IMMUNE BENEFITS

Luteolin is a plant flavonoid found in various herbs and vegetables, including parsley, olive oil, rosemary, and celery. Its benefits include neutralizing free radicals in the mitochondria as well as modulating the immune response.

Luteolin has also been shown to inhibit immune system cytokines implicated in the development and propagation of inflammation, including tumor necrosis factor alpha and interleukin-6.[49] Researchers in India have shown that luteolin reduces some of the inflammatory processes responsible for the airway constriction associated with asthma.[50] Still more interesting, Chinese researchers recently demonstrated that luteolin binds with the surface spike proteins on the deadly SARS virus, blocking its entry into the host cell. As a result, say the researchers, luteolin may represent an effective means of developing new drugs for the prevention of viral infections such as HIV, hepatitis C, and SARS.[51]

WHEAT SPROUT ENZYMES: ENHANCING MITOCHONDRIAL ENERGY

Wheat sprout enzymes are another source of bioactive plant flavonoids. Their potential benefits range from improving the symptoms of fibromyalgia and joint pain to increasing mitochondrial energy and relieving symptoms of chronic fatigue syndrome. These benefits are related to the presence of several potent natural antioxidant enzymes—including superoxide dismutase (SOD), glutathione peroxidase, and catalase—that offer powerful protection against the scourge of oxidative stress that can damage mitochondria, DNA, and cellular components, as well as contribute to the onset of disease.

Scientists have known for some time that inflammatory diseases are often associated with a decrease in antioxidant enzymes. For example, Korean researchers recently demonstrated that the activity of SOD and glutathione peroxidase is significantly lower among rheumatoid arthritis patients than among control subjects. The patients' dietary intake of antioxidants was also lower, the researchers discovered.[52]

Stanford University scientists recently noted a correlation between the presence of superoxide anion and the development of a wide range of degenerative diseases, including atherosclerosis, stroke, heart attack, chronic and acute inflammatory conditions, and "a variety of age-related disorders."[53] The pro-inflammatory superoxide anion is scavenged and neutralized by SOD.

The relationship among superoxide, SOD, and disease processes is so compelling that scientists attempted years ago to intervene in diseases such as osteoarthritis by injecting SOD derived from livestock blood cells directly into diseased joints. While the inflammation relief was often dramatic, the technique was somewhat impractical and has not been embraced as a treatment for human patients.[54]

Wheat sprout extract, on the other hand, represents a far more acceptable means of increasing one's levels of natural antioxidant enzymes. Italian researchers recently published an analysis of the antioxidant content of wheat sprout extract and found that the catalase and peroxidase activity appears to be very strong.[55] Another team of Italian scientists compared the antioxidant activity of wheat sprout extract to such antioxidants as ascorbic acid, quercetin, and reduced glutathione, and found that the "oxygen superoxide scavenging activity performed by wheat sprout extracts . . . is comparable to that shown by these pure compounds."[56]

CONCLUSION

Science has revealed that the mitochondria not only function as energy factories, but also play a vital role in the aging process, helping to determine the speed at which it progresses and influencing our health status along the way. Appropriate use of the nutrients shown to affect mitochondrial function therefore helps to maximize the body's defenses, positively influencing our longevity.

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