

COMBINED ALPHA-LIPOIC ACID AND ACETYL-L-CARNITINE SUPPLEMENTATION

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In this article, the authors discuss the effects of alpha-lipoic acid and acetyl-L-carnitine on Alzheimer's disease and ageing, and how these two supplements work in combination at the metabolic level

The recent use of alpha-lipoic acid and acetyl-L-carnitine as a combination therapy has been widely reported in the media and on the internet, and a range of products are available both in retail outlets and via the internet. The separate components have undergone several studies and may be useful in a variety of disease states.

ALPHA-LIPOIC ACID

Alpha-lipoic acid is an anti-oxidant found as a natural source in meat, liver and yeast,¹ and readily absorbed from the diet, but also synthesised by animals and humans. It is rapidly converted to dihydrolipoic acid (DHLA) in many tissues. DHLA acts synergistically with other anti-oxidants. It is a non-essential nutrient created by the human body and so deficiencies are not known to occur. Side-effects of supplementation with this product are rare, but skin rash and the potential for hypoglycaemia in diabetes patients are the most likely to occur.¹

ANTIOXIDANTS AND THE MECHANISM OF ALPHA-LIPOIC ACID ACTION

Oxidation during the process of normal metabolism causes extensive damage to DNA, proteins and lipids, which is thought to be a cause of ageing and degenerative disease. The body has numerous natural antioxidant defences, such as ascorbate (vitamin C) and tocopherol (vitamin E), and these help to limit the levels of reactive oxidants and the damage they cause. Enzymes also involved in this include superoxide dismutase and glutathione peroxidase.² These antioxidants can have a beneficial effect in many disease states, such as cancer, cardiovascular disease, immune system deficiencies, cataracts and brain dysfunction.³

Alpha-lipoic acid has been suggested as a possible candidate to be used specifically as an antioxidant, and has undergone several studies to demonstrate its use as a source of redox supplementation.⁴ It also appears to improve the recycling of other antioxidants, such as vitamin E, vitamin C, co-enzyme Q and glutathione.⁵

The possible beneficial actions of alpha-lipoic acid in a range of disease states has been investigated, including HIV,^{3,6} neurodegenerative diseases,³ Alzheimer's disease,⁷ depression,⁸ diabetes⁹ and radiation injury.³

ACETYL-L-CARNITINE

Acetyl-L-carnitine is structurally related to the natural amino acid L-carnitine and has some similar functions, but it is not technically an essential nutrient. It occurs naturally in the brain, liver and kidney, and is synthesised in mitochondria.¹⁰

It has been claimed that acetyl-L-carnitine is of use in increasing energy, losing weight, increasing immune function, enhancing and protecting mental faculties and also in lowering cholesterol. These claims are yet to be substantiated. However, the most important claimed benefit is in the treatment of age-related cognitive decline. Side effects of this compound are relatively uncommon and mild.¹¹

Primary deficiency of acetyl-L-carnitine is caused by impairment of the membrane transportation of carnitine, and symptoms may include chronic muscle weakness, recurrent episodes of coma and hypoglycaemia, as well as encephalopathy and cardiomyopathy. Inherited disorders of metabolism can lead to secondary deficiency of carnitine.¹²

As with alpha-lipoic acid, there have been numerous studies investigating the effects of the compound on different disease states, including HIV,⁶ Alzheimer's disease¹¹ and ageing.¹³

ALZHEIMER'S DISEASE

Oxidative stress and energy depletion are trademarks of Alzheimer's disease. As the body tries to degrade the senile plaques, it produces, among other products, free radicals. These lead to the damage of adjacent nerve tissues. Anti-inflammatory and antioxidant products are thought to delay the progression of Alzheimer's disease. The disease remains a neuropsychiatric disorder without widely accepted effective treatment or prevention.

Acetyl-L-carnitine has been investigated for beneficial effects in this disease and has been shown to slow the progression of symptoms.¹¹ It has few and mild side effects,¹⁰ which makes it potentially useful in

long-term therapy. It has been reported that acetyl-L-carnitine normalises alterations in membrane and energy metabolism and increases the levels of nerve growth factor in the CNS.¹¹

It has been demonstrated that acetyl-L-carnitine significantly slows the clinical rate of progression of the disease, and improves membrane phospholipid and high energy phosphate metabolism. It was found in Alzheimer's patients that the levels of phosphomonoesters (PME) decrease with progression of the disease, especially towards the degenerative phase, and treatment with acetyl-L-carnitine can increase the levels of PME. The decrease of PME can be explained by the decreased synthesis of membranes, including the membranes of synapses, where most energy in neurones is consumed. This results in decreased energy consumption in Alzheimer's patients. This whole process is reversed by treatment with acetyl-L-carnitine, which may be owing to acetyl-L-carnitine being able to increase the CNS levels and utilisation of nerve growth factor, causing increased synthesis of membranes.¹¹

The current treatments available for Alzheimer's disease inhibit anticholinesterase, and acetyl-L-carnitine has been considered for use because it is able to serve as a precursor for acetylcholine. Studies have demonstrated the ability of acetyl-L-carnitine to maximise energy production and promote cellular membrane stability. Therefore it is suggested that the beneficial effects of acetyl-L-carnitine are associated both with its cholinergic properties and also its effects at the mitochondrial level.¹²

There have been a number of studies undertaken using acetyl-L-carnitine in the treatment of Alzheimer's disease that have shown no benefit.¹¹ Therefore, the effects of acetyl-L-carnitine itself need to undergo further investigation.

AGEING

Acetyl-L-carnitine has numerous effects in many of the problems associated with ageing. It can be used in reversing the ageing of the heart by restoring its metabolic function and reversing the age related decline in cardiolipin levels. It may also be of use in brain protection and nerve regeneration by maintaining the cell's energy cycle, among other mechanisms. Acetyl-L-carnitine enhances the production of energy in the cells of the

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body, which can be of benefit in inhibiting the progression of age-related dysfunctions.¹³

COMBINATION THERAPY

The main area of development for the combination of these two products is in combating the signs of ageing associated with the inhibition of mitochondrial decay. There are various internet sites advertising the combination as the "amazing new anti-ageing supplements" and "the secret of youth". The combination product was claimed on the internet (www.directresponsemarketing.co.uk/antiageing) to combat free radicals, which can cause or contribute to the symptoms of ageing, from memory loss to wrinkles, by attacking the body's tissues. There have been many reports in the media on claimed effects of the combination product.

Availability of this supplementation in a twin pack is widespread, there being over 100 United Kingdom suppliers on the internet, and health food shops, both single and multiples, supply different manufacturer's products. Pharmacies specialising in complementary medicines supply twin packs, but it is possible that patients are also purchasing lipoic acid and acetyl carnitine (or carnitine) separately.

Memory tasks testing spatial and temporal memories have been undertaken in rats¹⁴ and performance in these tasks was shown to improve during combination supplementation. Oxidative damage to nucleic acids is also reduced and mitochondrial structural decay is reversed. The rats involved in one study were reported to show increased energy.¹⁵

HOW THEY WORK TOGETHER

Alpha-lipoic acid protects the cell and mitochondria by removing free radicals. Acetyl-L-carnitine is more potent in restoring mitochondrial energy production, but does not prevent the accumulation of free radicals.

Thus using these in combination is complementary, raising mitochondrial function while lowering free radical production. The combination therapy not only reduces the mitochondrial free radicals, but also boosts the activity of a damaged enzyme, carnitine acetyltransferase in rats. This enzyme plays a key role in burning fuel in mitochondria. It is the acetyl-L-carnitine that performs the latter mechanism. Carnitine acetyltransferase is less active in aged cells, and supplementation restores this function to levels similar to those in young cells.¹⁶

IMPROVING SUBSTRATE BINDING AFFINITY

Ageing is partly due to the production of oxidants during metabolism, and also associated with a decrease in cellular enzyme or receptor activities. Many gene mutations result in the corresponding enzyme having a poorer binding affinity for its coenzyme,

which lowers the rate of reaction. Increasing the concentration of the coenzyme partially restores the enzyme activity. This mechanism is used in reversing the mitochondrial decay of ageing.

Carnitine acetyltransferase (CAT) catalyses the reversible conversion of acetyl-CoA and carnitine to acetylcarnitine and CoA. CAT regenerates CoA and causes acetyl groups to enter the mitochondria for oxidation. CAT activity decreases with age, and also decreases in association with a number of disease states, all of which are related to ageing, such as Alzheimer's disease. There is an age associated decrease in CAT binding affinity for substrates and CAT activity. The addition of acetyl-L-carnitine along with alpha-lipoic acid, as a CAT substrate, partially reverses CAT inhibition.¹⁶

In aged rat brain cells, a study showed that CAT activity was decreased along with its binding affinity for acetyl-L-carnitine and Coenzyme A. Supplementation with acetyl-L-carnitine alone was shown to increase the levels of binding affinity for itself as a substrate, and supplementation with alpha-lipoic acid had a small effect on CAT activity. However, supplementation with the combination product restored both CAT activity and its binding affinity.¹⁶

It has been suggested that the loss of binding affinity associated with ageing may be due to the interaction of aldehyde products of lipid peroxidation with the protein. Brain malondialdehyde (MDA) levels increase with age, which has the effect of decreasing the binding affinity and the V_{max} of CAT, therefore contributing to enzyme inactivation. Alpha-lipoic acid and acetyl-L-carnitine lower the levels of the aldehydes produced from lipid peroxidation, especially MDA, but this is not the only explanation for their effects on improving CAT function. Alpha-lipoic acid was shown to lower the MDA levels, which has a small effect on increasing binding affinity and enzyme function, while the acetyl-L-carnitine restores CAT function to a much greater extent. Alpha-lipoic acid is therefore synergistic when used with acetyl-L-carnitine.¹⁶

The brain tissue of aged rats was shown to have increased levels of copper and iron accumulation. This can lead to oxidative damage by catalysing oxidant generation and lipid peroxidation. In these particular studies, the combination product did not have a significant effect on transition metal accumulation, but this is a possibility that cannot entirely be ruled out. The product may have an effect by chelating the free transition metals in the brain, therefore inhibiting oxidative damage. Alpha-lipoic acid is an efficient chelator of copper and iron and further studies in this area are warranted.¹⁶

IMPROVING METABOLIC FUNCTION AND DECREASING OXIDATIVE STRESS

Having decided that mitochondrial decay by the release of reactive oxygen species during electron transport, leading to a vicious cycle of increasing mitochondrial damage, is a significant factor in ageing, many studies have been designed and carried out into the

effects of antioxidants on the ageing process. The vicious cycle leads to decreased cell function and also a reduction in the amount of ATP produced, causing a drop in energy levels.¹⁵

In one particular study, alpha-lipoic acid was chosen as a supplement because of its antioxidant properties and being able to increase the levels of endogenous antioxidants. Acetyl-L-carnitine was chosen because it is a mitochondrial metabolite and can reverse the age-related decline in carnitine levels in the tissues.

It was suggested that acetyl-L-carnitine improves mitochondrial function and increases general metabolic activity. Unfortunately, it was observed that supplementation with high levels of acetyl-L-carnitine lowered the hepatocellular antioxidant status, but this was not observed in any other tissues, nor when supplemented at lower levels. High doses saw an increase in mitochondrial oxidant flux, suggesting supplementation increases of the flow of electrons through the electron transport chain, heightening the formation of reactive oxygen species. This suggested the idea of supplementing acetyl-L-carnitine with alpha-lipoic acid.¹⁵

It was shown that acetyl-L-carnitine improved the average mitochondrial membrane potential to a level similar to that in young rat cells. This was caused by the replenishment of carnitine levels, which increased the amount of fatty acids brought into the cells for β -oxidation. It also prevents the age-related decline in cardiolipin levels, which is beneficial to the cell since this decline adversely affects the mitochondria. Acetyl-L-carnitine does not improve the age-related increase in antioxidants, so the supplementation of alpha-lipoic acid is of vital importance to maximise the benefits of this therapy. Increased oxidant leakage occurs with age as electron transfer becomes less efficient and acetyl-L-carnitine supplementation also causes a small but significant increase in oxidant appearance, as well as reducing the levels of antioxidants in the liver cells.¹⁵

Alpha-lipoic acid was shown to be taken up easily into a variety of tissues, where it is reduced to DHLA. Both of these compounds induce cysteine uptake, which causes an increase in glutathione synthesis. It maintains and reverses the decline in hepatocellular and myocardial ascorbate and glutathione levels associated with ageing, and so is of great help in the general upkeep of the body's antioxidant status. Alpha-lipoic acid also induced some other cell responses that complement the actions of acetyl-L-carnitine.

The two compounds act synergistically to improve both fatty acid and glucose catabolism and also to improve energy production. These reactions occur along with the amelioration of oxidative stress, loss of metabolic function and mild cognitive impairment.¹⁵

REVERSAL OF MEMORY LOSS AND MITOCHONDRIAL DECAY

It is known that accumulation of oxidative damage to mitochondria, protein and nucle-

ic acid in the brain may lead to cognitive dysfunction. Oxidative damage increases with age in the hippocampus, which is an area of the brain important in memory. Therefore, memory has been shown to decrease with age and, in conditions such as Alzheimer's disease, this loss is increased. Memory loss is accompanied by the accumulation of oxidative damage to lipids, proteins and nucleic acids, and also by mitochondrial decay. Alpha-lipoic acid affects the utilisation of carbohydrates involved in ATP production in mitochondria, and is also of use because of its antioxidant properties. Acetyl-L-carnitine is involved in transport of fatty acids for oxidation and ATP production. It improves cognitive function and neuronal bioenergetic mechanisms.¹⁴

In a study carried out to investigate the effect of acetyl-L-carnitine and alpha-lipoic acid on memory loss, spatial and temporal memory were tested.¹⁴ Oxidative damage is associated with cognitive deficits in both spatial and temporal memory. Both types of memory rely on the hippocampus, but temporal memory also relies on the striatum and cerebellum. Spatial memory decreases with age but this study showed that supplementation with the combination of acetyl-L-carnitine and alpha-lipoic acid restored some of this function. Each compound was found to restore this function to a small extent but the combination use was significantly more effective. The combination product can reduce mitochondrial dysfunction in peripheral systems such as the sensory systems. The reverse effect seen in these systems may be linked with a reverse in the age-related decline in nervous, cardiovas-

cular, visual and auditory systems, as well as effects on motivation and physical strength.¹⁴

Temporal memory measures the function of learning processes, attention and exploratory behaviour. Peak rate is the term used to measure the decline in this function. It reflects the change in a response learning mechanism. The older rats involved in the study showed lower peak rates, suggesting difficulty in learning the relevant response. Use of the combination product showed a complementary effect on improving the peak rates.¹⁴

This particular study tested the theory that the cognitive improvements due to supplementation were linked to reductions in oxidative damage. RNA oxidation is increased significantly as a function of age and neuronal RNA oxidation is an aspect of Alzheimer's disease, Parkinson's and Down's syndrome, which are all diseases involving severe cognitive deficits. Therefore, treatment with this supplement would have a beneficial effect on reducing the levels of oxidation in these situations. Also, the cognitive improving effect of this supplement may be caused in part by the donation of an acetyl group for the synthesis of acetylcholine through choline acetyltransferase and CAT. This improves cognitive function, since low levels of acetylcholine are associated with age-related cognitive dysfunction.¹⁴

CONCLUSION

In old rats, compared with young rats, mitochondrial membrane potential, cardiolipin levels, respiratory control ratio and overall cellular oxygen consumption

decline, and the level of oxidants increases. The level of mutagenic aldehydes from lipid peroxidation is also increased. Ambulatory activity of old rats is markedly lower than that of young rats. The normal mitochondrial metabolites acetyl carnitine (a substrate for acetylcarnitine transferase) and alpha-lipoic acid (a coenzyme for pyruvate and α -ketoglutarate dehydrogenases), when fed to old rats for a few weeks, restored mitochondrial function and lowered the level of oxidants to that of young rats, and also increased the ambulatory activity. One plausible mechanism might explain the effect of these two metabolites. Increased oxidative damage with age to proteins and the lipids in membranes causes a deformation of the structure of key enzymes, with a consequent worsening of affinity for their substrates or cofactors; thus, an increased concentration of the substrate restores the velocity of the enzymatic reaction, which restores function.¹⁷

Use of alpha-lipoic acid and acetyl-L-carnitine in combination is of primary interest in anti-ageing therapy in order to prevent the symptoms associated with growing old. Widely circulated claims are only partially justified since the majority of the studies that were performed involving this combination of supplements have been carried out on rats. Although combining acetyl-L-carnitine and alpha-lipoic acid appears to improve memory loss, decrease oxidative stress, improve metabolic function and decrease mitochondrial decay in rats, greater study is required to be able to be more specific on the precise benefits held by this combination product and the long-term side-effects in humans.

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