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ORIGINAL ARTICLE

Efficacy of levo carnitine and alpha lipoic acid in ameliorating the decline in mitochondrial enzymes during aging

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Summary
Background: Mitochondria are central to energy production and are therefore fully integrated into the rest of the cell's physiological responses to stress. The age-related decline of capacity of each cell to manufacture energy (as ATP) is due to the progressive loss of structural integrity of mitochondria. It is apparent that as the body ages, the cells become less and less able to maintain threshold levels of cellular energy production.
Methods: In the present study we have evaluated the efficacy of carnitine, a mitochondrial metabolite and lipoic acid, a potent antioxidant on the activities of the tri carboxylic acid (TCA) cycle enzymes like succinate dehydrogenase, malate dehydrogenase, α-ketoglutarate dehydrogenase, Isocitrate dehydrogenase and electron transport complex I–IV in young and aged heart mitochondria.
Result: We observed that there was an age-dependent decrement in the levels of the TCA cycle enzymes and electron transport chain complexes. Supplementation of carnitine (300 mg/kg bw/day) and lipoic acid (100 mg/kg bw/day) for 30 days brought the activities of these enzymes to almost near normal levels.
Conclusion: These findings suggest that the combination of these drugs raises the mitochondrial energy producing capabilities by reversing the age-associated decline in mitochondrial enzyme activities and thereby protecting mitochondria from aging.

Introduction

Aging is a multifactorial phenomenon characterized by time-dependent decline in physiological function, which varies between different species.

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Several theories have been proposed to explain this process. The free radical theory first proposed by Harman[1] hypothesized that free radicals produced during aerobic respiration cause cumulative oxidative damage to proteins, lipids and DNA resulting in aging and death. It also predicts that slowing the rate of initiation of free radical reactions can modulate the aging process.[2–4] Many of the significant age-related changes are exhibited in post-mitotic tissues such as brain, heart and skeletal muscle.

The heart is dependent on molecular oxygen and oxidative phosphorylation to provide high-energy compounds necessary for contraction, but this exposes the myocardium to harmful reactive oxygen species that are generated continuously as normal by-products of the mitochondrial electron transport chain (ETC). The aging heart undergoes significant functional and structural alterations leading to atrophy and a compensatory hypertrophy, followed by myocardial fibrosis.[5] In addition, there is an age-related decline in the capacity to withstand stress, such as ischemia/reperfusion.[6] In its most severe form, cardiac decay results in congestive heart failure, one of the leading causes of death in people over the age of 65. Although the mechanisms underlying cardiac decay are not clear, loss of mitochondrial function and a resultant increase in oxidative stress has been proposed to be one of the key factors in myocardial aging.[7] Therefore, it seems very likely that age-related changes at the mitochondrial level are important in the decline of physiological function that accompanies senescence.

The mitochondrial ETC plays an important role in energy production in aerobic organisms. Electrons from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), produced during the citric acid cycle, flow down the ETC and are coupled to the establishment of a proton gradient that is utilized in the production of ATP. The final electron acceptor is molecular oxygen, which through four-electron reduction is converted to H_2O. The ETC is located in the inner membrane of the mitochondria and consists of five complexes. They are: NADH dehydrogenase (Complex I), Succinate dehydrogenase (Complex II), cytochrome *bc*1 complex (Complex III), cytochrome *c* oxidase (Complex IV) and ATP synthase (Complex V). However, as mitochondria including the respiratory chain become more and more damaged, higher amounts of free radicals are generated. This kind of a vicious cycle finally leads to non-functional mitochondria.

Carnitine is a natural substance that acts as a carrier of fatty acids across the inner mitochondrial membrane for subsequent β-oxidation. L-carnitine and its esters are endogenously synthesized in man and also found in diet.[8] Carnitines are essential cofactors of several enzymes necessary for the transformation of long chain fatty acids. Thus, we chose to administer carnitine to aged rats to improve the mitochondria-mediated bioenergetics. But despite the benefits of carnitine treatment, there are also potential adverse effects. While carnitine supplementation reversed many of the altered characteristics evident in mitochondrial metabolism with age, the rate of oxidant production was higher in carnitine-supplemented rats.[9]

We further observed that the age-related increase in oxidant production and oxidative damage can be reversed by co-supplementation with α-lipoic acid, a disulfide compound found naturally in plants and animals.[10] The disulfide form of lipoic acid is reduced in mitochondria by specific dehydrogenase and its supplementation would thus target an antioxidant to the mitochondria, the major site of free radical production.[11] Supplementation with LA may also boost mitochondrial function because it is a co-factor for pyruvate and α-ketoglutarate dehydrogenase[12,13] and as such, may be a useful dietary supplement in its own right to increase overall mitochondrial metabolism. In the present study, we have observed the changes in the activities of mitochondrial enzymes in aged rats and the effect of co-supplementation of carnitine and lipoic acid on these enzymes.

Materials and methods

Source of chemicals

L-Carnitine and DL-α-lipoic acid were purchased from Sigma chemical company (St. Louis, MO, USA). All other chemicals were of reagent grade and were obtained from Glaxo Laboratories, CDH division, Mumbai, India and Sarabhai. M. Chemicals, Baroda, India.

Animals

Male albino rats of Wistar strain approximately 3–4-months-old (young) and above 24-months-old (aged) were used in this study. They were healthy animals procured from The King's Institute of Preventive Medicine, Chennai. The animals were housed in large spacious cages and were given food and water ad libitum. The animal room was well ventilated and had 12 h light/dark cycles throughout the experimental period. The animals were maintained on a commercial rat feed which