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Review

Mineral and vitamin deficiencies can accelerate the mitochondrial decay of aging

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Abstract

Mitochondrial oxidative decay, which is a major contributor to aging, is accelerated by many common micronutrient deficiencies. One major mechanism is inhibition of the pathway of heme biosynthesis in mitochondria, which causes a deficit of heme-*a*. Heme-*a*, only found in Complex IV, is selectively diminished, resulting in oxidant leakage and accelerated mitochondrial decay, which leads to DNA damage, neural decay, and aging. We emphasize those deficiencies, which appear to cause damage through this mechanism, particularly minerals such as iron (25% of menstruating women ingest <50% of the RDA) or zinc (10% of the population ingest <50% of the RDA). Several vitamin deficiencies, such as biotin or pantothenic acid, also increase mitochondrial oxidants through this mechanism. Additionally, other minerals such as magnesium and manganese that play a role in mitochondrial metabolism, but do not affect heme directly, are discussed. An optimum intake of micronutrients could tune up metabolism and give a marked increase in health, particularly for the poor, elderly, and obese, at little cost.

Abbreviations: RDA, Recommended daily allowance; ATP, Adenosine triphosphate; TCA, Tricarboxylic acid cycle; FC, Ferrochelatase; δ-ALAD, δ-Aminolevulinate dehydratase; δ-ALA, δ-Aminolevulinic acid; PLP, Pyridoxal 5′-phosphate; δ-ALAS, δ-Aminolevulinic acid synthetase; CoA, Coenzyme A; PDH, Pyruvate dehydrogenase; α-KGDH, α-Ketoglutarate dehydrogenase; FAD, Flavin adenine dinucleotide; NAD, Nicotinamide adenine dinucleotide; PPO, Protoporphyrinogen oxidase

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Contents

1. Mitochondrial decay with age

Mitochondria are the most complex organelles in the cell; they provide energy for basic metabolic processes, detoxify oxygen, provide essential metabolism such as heme biosynthesis, function in calcium (Ca) and iron (Fe) homeostasis, and play a key role in programmed cell death. Oxidants are produced as inevitable byproducts of mitochondrial function. Mitochondria are particularly vulnerable to this damage as they are the sites of oxidant leakage and contain their own DNA. During aging, oxidation deforms many proteins in mitochondria, thereby decreasing their function directly or indirectly by lowering their affinity for their substrates or coenzymes (Liu et al., 2002c; Ames et al., 2006). Mitochondria have defenses against oxidants such as manganese (Mn) superoxide dismutase and selenium (Se)-containing GSH peroxidase, though optimum activity of these defenses requires adequate manganese and selenium in the diet. Cells also defend themselves from oxidants leaking from damaged mitochondria, in part, by their lysosomes degrading defective mitochondria, though this defense system also declines markedly in efficiency with age (Terman and Brunk, 2004). The decay of mitochondria with age impairs cellular metabolism. Mitochondrial membrane potential and cellular oxygen consumption decline with age, and oxidant production increases (Harman, 1972; Shigenaga et al., 1994; Hagen et al., 2002a). Oxidant damage to DNA (Beckman and Ames, 1998a,b; Attardi, 2002; Lee and Wei, 2005; Short et al., 2005), RNA (Liu et al., 2002b), proteins (Stadtman and Levine, 2000), and lipids in membranes are most likely involved in this decay, resulting in functional decline that compromises mitochondrial ability to meet cellular energy demands and other metabolic needs. This oxidative mitochondrial decay appears to be the major contributor to aging and the degenerative diseases of aging (Harman, 1972; Shigenaga et al., 1994; Hagen et al., 1997; Beckman and Ames, 1998a,b; Helbock et al., 1998).

We have made progress in reversing some of the mitochondrial decay in old rats by feeding them the normal mitochondrial metabolites acetyl carnitine or *R*-lipoic