Available online at www.sciencedirect.com
SCIENCE DIRECT
Experimental Gerontology 40 (2005) 369–376
Experimental Gerontology
www.elsevier.com/locate/expgero

Mini Review

Effect of dietary polyunsaturated fatty acids on age-related changes in cardiac mitochondrial membranes

Salvatore Pepe[a,b,c,d,*]

[a]Department of Cardiothoracic Surgery, Alfred Hospital, Melbourne, Vic., Australia
[b]Wynn Department of Metabolic Cardiology, Baker Heart Research Institute, Melbourne, Vic., Australia
[c]Department of Physiology, University of Melbourne, Melbourne, Vic., Australia
[d]Department of Surgery, Monash University, Melbourne, Vic., Australia

Received 27 February 2005; received in revised form 9 March 2005; accepted 10 March 2005
Available online 7 April 2005

Abstract

Remodeling of myocardial cell membranes is a major feature of advanced age. Mitochondrial function, crucial to sustaining energy production and management of myocardial metabolism, is impacted by age-dependent remodeling and ultimately exhibits a diminished threshold for excess Ca^{2+} buffering during events that stimulate increased myocardial Ca^{2+}, such as augmented cardiac work, oxidative stress or post-ischemic reflow. Relative Ca^{2+} intolerance, augmented superoxide formation and reduced efficiency in the management of reactive oxygen species, are important mitochondrial factors (of many) that are apparent in senescence and predispose the myocardium to be more vulnerable to ischemic injury. In addition to cell death, surviving myocytes increase in size and exhibit altered gene expression of key effector proteins, including those that sustain Ca^{2+} homeostasis. Age-associated mitochondrial membrane changes include increases in membrane rigidity, cholesterol, phosphatidylcholine, omega-6 polyunsaturated fatty acids (PUFA), 4-hydroxy-2-nonenal, and decreases in omega-3 PUFA and cardiolipin. These effects have been shown in animal studies to be exaggerated by diet rich in long chain omega-6 PUFA (i.e., arachidonic acid), and have profound consequences on the efficacy of membrane proteins involved with ion homeostasis, signal transduction, redox reactions and oxidative phosphorylation. However, some of the age-related detrimental adaptations may be beneficially modified by dietary strategy. Diet rich in omega-3 PUFA reverses the age-associated membrane omega-3:omega-6 PUFA imbalance, and dysfunctional Ca^{2+} metabolism, facilitating increased efficiency of mitochondrial energy production and improved tolerance of ischemia and reperfusion.

Keywords: Omega-3 polyunsaturated fatty acids; Cardiolipin; Mitochondria; Heart; Ischemia; Aging

1. Introduction

The senescent myocardium, compared to hearts from young adults, exhibits numerous structural, physiological and biochemical features, which include a reduction in the number of myocytes, cell enlargement and alteration of metabolic, ionic and electrical properties of myocytes. The aged heart is more likely to manifest reduced efficiency in oxygen utilization, reduced efficiency in mechanisms to detoxify or minimize production of reactive oxygen species (ROS), and reduced capacity to invoke 'ischemic preconditioning-like' intracellular signal transduction for post-stress survival (Hansford, 1983; Anversa et al., 1990; Olivetti et al., 1991; Lakatta, 1992; Walker et al., 1993; Lakatta, 1993; Di Lisa et al., 1998; Pepe et al., 1999, 2001; Lesnefsky 2001; Lakatta, 2003; Lakatta and Levy, 2003). As the energy requirement of myocardial excitation-contraction coupling during cardiac work is predominantly supported by mitochondria, they play a key role in the onset of age-associated changes in ion homeostasis-dependent processes supporting heart metabolism and contractile function. The aim of this brief review is to describe how specific age-linked changes to cardiac mitochondrial membrane lipids can influence crucial mitochondrial

* Address: Head, Laboratory of Cardiac Surgical Research, Alfred Hospital & Baker Heart Research Institute, POB 6492 St Kilda Rd. Central, Melbourne, Vic. 8008, Australia. Tel.: +61 3 85321310; fax: +61 3 85321314.
E-mail address: spepe@baker.edu.au.

0531-5565/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.exger.2005.03.005

processes that are perturbed in ischemia, and contribute to a reduced cellular capacity to recover from reperfusion injury. Although it is yet to be determined whether aged-linked mitochondrial dysfunction is a cause or consequence of aging, mitochondrial membranes, as indeed all cell membranes, undergo age- and diet-dependent remodeling of membrane phospholipid and fatty acid composition that impacts mitochondrial function and the heart's adaptive responses to stress and survival.

2. Post-ischemic loss of Ca^{2+} homeostasis is augmented with age

During each cycle of cardiac myocyte excitation and contraction, Ca^{2+} influx occurs and triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) via Ca^{2+} release channels (Lakatta, 1992, 2003). Ca^{2+} -induced- Ca^{2+} release results in a transient rise of cytosolic Ca^{2+} (Ca_i) and triggers activation of contractile proteins until Ca^{2+} is returned to the SR by Ca^{2+}-ATPase pumps or extruded from the cell by Na^+–Ca^{2+} exchangers (Froehlich et al., 1978; Schmidt et al., 1999). With increased age, a Ca^{2+}-dependent increase in diastolic relaxation time occurs partly due to a reduced removal of cytosolic Ca^{2+} by the SR pump and Na^+–Ca^{2+} exchanger (Froehlich et al., 1978; Narayanam et al., 1981; Heyliger et al., 1988; Heyliger et al., 1989; Josephson et al., 1991), and thus contribute to the augmentation and prolongation of the Ca_i transient (Lakatta, 1992; 2003).

Work conditions that demand increased cardiac output trigger catecholamine release from neurons ending in the heart to stimulate increased Ca^{2+} influx, oxygen consumption, ATP synthesis and a greater force of contraction. With the rise in intracellular Ca^{2+}, increased mitochondrial Ca^{2+} (Ca_M) uptake and activation of Ca^{2+}-dependent pyruvate dehydrogenase occurs to drive the maintenance of NADH/NAD^+, proton motive force (the H^+ electrochemical gradient, $\Delta\mu H$), and membrane potential ($\Delta\Psi_m$), across the inner mitochondrial membrane respiratory chain, and stimulates a greater rate of ATP synthesis (Gunter and Pfeiffer, 1990; Hansford, 1994; Lesnefsky et al., 2001; Di Lisa et al., 1998).

A common feature of cardiac ischemia and reperfusion during advanced age is increased vulnerability to the perturbation of Ca^{2+}-management systems resulting in highly elevated intracellular Ca^{2+} that precipitates systolic and diastolic contractile dysfunction (Hano et al., 1995). Although brief ischemia perturbs Ca^{2+} homeostasis, Ca_M buffering reserve permits normal function that is only infringed by prolonged ischemia and Ca^{2+} 'overload' at supra-micromolar levels, particularly upon reperfusion (Miyata et al., 1991, 1992; Ferrari, 1996). This breach has consequences for a variety of related mitochondrial effects, many of which are facilitated and enhanced by advanced age: reduced efficiency of Ca_M handling, increased permeability of the inner mitochondrial membrane to solutes occurs causing mitochondrial swelling, 'proton leak', decreased ADP-induced oxygen consumption, prolonged conversion of ADP to ATP, reduced oxidative phosphorylation rates and a degree of uncoupling between respiration and ATP synthesis (Ferrari, 1996; Di Lisa et al., 1998; Halestrap et al., 1998; Pepe et al., 1999; Jahangir et al., 2001). Such uncoupling causes reduced efficiency of oxygen utilisation and augmented free radical production (Nohl et al., 1978; Sawada and Carlson, 1997; Sohal et al., 1990; Papa and Skulachev, 1997; Rosenfeldt et al., 1999; Ambrosio et al., 1993; Droge, 2002a,b; Turrens, 2003).

Besides Ca^{2+}-overload, post-ischemic appearance of markers predictive of irreversible cell injury include: increased acidosis and P_i; decreased superoxide dismutase activity; accumulation of free radicals; activation of phospholipases; accumulation of long-chain acyl CoA and toxic products of membrane lipid peroxidation; and formation of protein adducts (Ferrari, 1996; Di Lisa et al., 1998; Halestrap et al., 1998; Pepe et al., 1999; Jahangir et al., 2001; Esterbauer et al., 1991; Lapidus and Sokolov, 1994; Blasig et al., 1995; Lucas and Szweda, 1998, 1999; Droge et al., 2002b). After sustained, severe ischemia, diminished ATP supply results in complete loss of intracellular Ca^{2+} homeostasis, which may result in ventricular fibrillation (Lakatta, 1992; Ferrari, 1996). At such excessive levels of Ca_M, the mitochondrial membrane permeability transition (MPT) is more likely to occur (Halestrap et al., 1998; Bernardi, 1999).

3. Potential triggers of MPT are increased with age

Ca_M-dependent cyclophilin-D binding to adenine nucleotide translocase facilitates conformational changes that cause adenine nucleotide translocase to form a non-specific pore (Halestrap et al., 1998, 2004; Crompton, 2004; Bernardi, 1999). The 'MPT pore' is presently considered to be a multi-protein complex that includes a voltage dependent anion channel. Cyclophilin-D binding is increased following augmented oxidative stress (and/or thiol agents from lipid peroxidation products) that sensitizes the MPT to Ca^{2+}. Mitochondrial matrix adenine nucleotide binding to adenine nucleotide translocase decreases the sensitivity of the MPT to Ca^{2+}. However, this substrate-dependent reduction in Ca^{2+} sensitivity may be diminished by products of lipid peroxidation that modify specific thiol groups on adenine nucleotide translocase, to the extent that $\Delta\Psi_m$ may be attenuated, ATP synthesis fails and MPT is enhanced (Halestrap et al., 1998, 2004; Bernardi, 1999). In addition to Ca_M, P_i, long-chain acyl CoA, adenine nucleotides, the redox state of specific protein thiols, and ROS also stimulate opening of the MPT pore that depolarises the mitochondrion and dissipates $\Delta\Psi_m$ preventing oxidative phosphorylation (Halestrap et al., 2004; Lapidus and Sokolov, 1994). Following the collapse of