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Review

Bioenergetics of the aging heart and skeletal muscles: Modern concepts and controversies

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ABSTRACT

Age-related alterations in the bioenergetics of the heart and oxidative skeletal muscle tissues are of crucial influence on their performance. Until now the prevailing concept of aging was the mitochondrial theory, the increased production of reactive oxygen species, mediated by deficiency in the activity of respiratory chain complexes. However, studies with mitochondria *in situ* have presented results which, to some extent, disagree with previous ones, indicating that the mitochondrial theory of aging may be overestimated. The studies reporting age-related decline in mitochondrial function were performed using mainly isolated mitochondria. Measurements on this level are not able to take into account the system level properties. The relevant information can be obtained only from appropriate studies using cells or tissue fibers.

The functional interactions between the components of Intracellular Energetic Unit (ICEU) regulate the energy production and consumption in oxidative muscle cells. The alterations of these interactions in ICEU should be studied in order to find a more effective protocol to decelerate the age-related changes taking place in the energy metabolism.

In this article, an overview is given of the present theories and controversies of causes of age-related alterations in bioenergetics. Also, branches of study, which need more emphasis, are indicated.

Contents

Abbreviations: AK, adenylate kinase; AMPK, AMP-activated protein kinase; ANT, adenine nucleotide translocase; CI-IV, respiratory chain complexes I–IV; CM, cardiomyocyte; CK, creatine kinase; EFP, early filling percentage; HK, hexokinase; ICEU, Intracellular Energetic Unit; LDH, lactate dehydrogenase; mtDNA, mitochondrial DNA; MHC, myosin heavy chain; MI, Mitochondrial Interactosome; MOM, mitochondrial outer membrane; MtCK, mitochondrial creatine kinase; OXPHOS, oxidative phosphorylation; PCr, phosphocreatine; RC, respiratory chain; RCSC, respiratory chain supercomplex; ROS, reactive oxygen species; SC, satellite cells; SR, sarcoplasmic reticulum; TSR, torsion to shortening ratio; VDAC, voltage-dependent anion channel.

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1. Introduction

The progressive aging of the world population demonstrates a continuous upward trend. According to the United Nations Population Division report, the global share of older people (aged 60 years and older) rose from 8% in 1950 and 9% in 1990 to 12% in 2013, and will further increase to 21% by 2050. The part of the population over 80 years is also growing sharply, rising from 69 million to 379 million by 2050 (Harper, 2014; Mahishale, 2015). Aging increases a probability factor of developing many diseases, such as atherosclerosis and cardiovascular diseases, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension, and Alzheimer's and Parkinson diseases (Belsky et al., 2015; Blagosklonny, 2009; Gurland et al., 1999; Harvey et al., 2015; Wang and Shah, 2015; Wang et al., 2015).

Aging is a well-known contributing factor for heart failure, which is the leading cause of death world-wide (Olivetti et al., 1991; Shih et al., 2011). Older persons experience a myocardial infarction more often than younger (Shih et al., 2011). Moreover, it was recently proposed to include the concept of cardiovascular aging as a disease in the practice of clinical medicine (Lakatta, 2015). Previous studies have shown that cardiac aging is associated with a number of pathophysiological alterations, both at cellular and tissue levels, including left ventricular hypertrophy (associated with a profound decrease in the heart beat rate and strength), arrhythmia, changes in ventricular chamber volume, accumulation of extracellular matrix, fibrosis, a step-by-step decay in cardiac reserve capacity (associated with a reduction in the total number of cardiomyocytes (CMs), dysfunction of heart fibroblasts and other abnormalities (Gray, 2005; Olivetti et al., 1991; Papp et al., 2012; Yechiel et al., 1986)).

Along with heart failure, one of the hallmarks in human aging is sarcopenia, the degenerative loss of skeletal muscle mass with a concomitant decline in muscle strength leading to a progressive decrease in mobility and quality of life. However, the etiology of sarcopenia is rather complex, involving central and peripheral nervous system alterations, hormonal changes, nutritional, immunological (inflammation) and physical activity changes, and mechanistic explanations for it have remained poorly defined as yet (Narici and Maffulli, 2010). At the cellular level, the oxidative stress and changes in mitochondrial metabolism may be an important contributor to the disease development (Beltran Valls et al., 2015; Johnson et al., 2013; Lourenco Dos Santos et al., 2015). However, the cellular and molecular mechanisms involved in the age-mediated dysfunction of different striated muscle cells are not completely understood.

Cardiac and oxidative skeletal muscle cells have a permanent demand for energy, which is mainly supplied through the oxidative phosphorylation (OXPHOS) system (Guzun et al., 2015; Saks et al., 2008a). Therewith mitochondria play a central role in the functioning of cardiac and skeletal muscles cells, including besides ATP production, calcium homeostasis, reactive oxygen species (ROS) generation, and apoptotic signaling (Saks et al., 2014). Now there is evidence that mitochondrial dysfunction may be one of the significant factors responsible for heart failure and skeletal muscle weakness in old age (Gray, 2005; Miljkovic et al., 2015). However, the knowledge of the causes and the severity of age-related disturbances in the metabolism of cardiac and skeletal muscles mitochondria is still contradictory (Picard et al., 2010; Rasmussen et al., 2003).

This situation could be largely related with differences in the used model systems and experimental approaches. To date, the overwhelming number of studies on the bioenergetics of the aging heart were performed on isolated mitochondria, but this approach led to artifact conclusions, since the procedure of isolation of these organelles itself can damage the mitochondria (Picard et al., 2011). Also, when applying isolated mitochondria, the complexity of their intracellular structural organization, dynamics and regulation of mitochondrial metabolism within a myocyte or at the heart tissue are not considered (Ieda, 2013). These factors, however, play a detrimental role in the bioenergetic function of mitochondria in cardiac and skeletal muscle cells (Guzun et al., 2015; Kuznetsov et al., 2008; Saks et al., 2014; Varikmaa et al., 2014).

Thus, in the present review, the age-related alterations in the energy homeostasis of cardiac and skeletal muscle cells will be considered in the light of System Molecular Bioenergetics and the concept of Intracellular Energetic Units (ICEUs) (Guzun et al., 2015). The System Bioenergetics approach takes into account: (1) the integration of physiological and biochemical processes at cellular, tissue and organ levels; (2) the complexity of intracellular interactions of mitochondria with sarcoplasmic reticulum and other cellular structures, especially with cytoskeleton components; and (3) compartmentalization of intracellular energy producing/transfer systems and signal transduction pathways for regulation of energy fluxes.

In view of the importance of the problems described above, the aim of this review is to summarize the contemporary experimental observations and hypotheses about the mechanism(s) of the age-mediated decline in the functioning of cardiac and skeletal muscles at both the cellular and tissue levels. Additionally, possible gender-specific differences in muscle aging will be discussed.

2. Aging: general concepts, causes and effects

The main questions concerning aging are: what are the metabolic changes that influence the quality of our life in senescence most and when they emerge. The period of aging in a species' lifetime could be defined by increased mortality rate caused by the increased number of emerged illnesses. In humans the turning point of the mortality curve is at the age of 45 (Kaeberlein et al., 2001). Also, in aged organisms the reduced adaptability to the environmental and metabolic stimuli can be observed. At the organ level, even during healthy aging, changes in biochemical composition and decrease in physiological capacity take place (Troen, 2003). For example, the total skeletal muscle and bone mass decreases during aging.

The exact causes of aging are unknown yet and currently, there are two prevalent sets of theories of its origin. One set is stochastic theories, which propose that the reason behind aging may be: (1) random damage to vital molecules or (2) developmental, which posts that the length of our life is genetically preprogrammed: life includes phases of development, maturation and aging (Troen, 2003). The stochastic theories comprise the accumulation of post-translational modifications of proteins, random errors in DNA synthesis, and elevated ROS production as the main triggers of aging. The latter can damage mitochondrial respiratory chain (RC) complexes, cause cellular energetic depression and increase ROS production, which leads to the mitochondrial DNA (mtDNA) damage and insufficient energy balance (Beckman and Ames, 1998; Sohal, 2002; Tatarkova et al., 2011). Several studies