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Energy metabolism in the aged heart

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Abstract

Aging is associated with a decline in energy production in the heart that can compromise the ability of the heart to adapt to stresses requiring an increase in energy demand. The main source of energy for the heart arises from mitochondrial oxidative phosphorylation. With aging, mitochondrial function becomes compromised, which can lead to a decrease in energy production and an increase in the production of reactive oxygen species. Impaired energetics in the aging heart can result not only from impaired mitochondrial ATP production, but also from a decrease in metabolic flexibility in the type of fuel used by the heart for energy production, as well as a decreased efficiency of ATP transfer from the site of mitochondrial production to the site of use. Improving both cardiac energy production and the efficiency of energy production may be a novel therapeutic approach to lessen cardiac disease in the elderly. ■

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Introduction

It has been well established that aging is a major contributor to the probability of developing cardiovascular diseases, which includes a marked increase in the incidence and severity of heart failure.[1,2] Aging also results in a number of pathophysiological alterations in the heart, both at a cellular and tissue level, that contribute to an increased risk of developing cardiovascular disease,[1-3] which includes the development of cardiac hypertrophy, arrhythmias, and left ventricular dilatation, as well as alterations in the extracellular matrix, increased cardiomyocyte loss, alterations in calcium homeostasis, apoptotic signaling, autophagy, reactive oxygen species (ROS) generation, and many other key metabolic pathways in the heart.[4] In addition, aging results in dramatic changes in energy homeostasis in the heart, which includes the development of mitochondrial dysfunction.[5] These alterations in energy metabolism are likely to be important contributors to the development of cardiovascular diseases in the aging population. Despite this, our understanding of what effect aging has on cardiac energy metabolism is incomplete and still contradictory. This paper reviews what is known with regard to the effects of aging on cardiac energy metabolism.

Aging effects on mitochondrial function

The heart has a very high energy demand and must produce large amounts of energy, in the form of adenosine triphosphate (ATP), to sustain contractile function.[6] The majority of this ATP production originates from mitochondrial oxidative phosphorylation.[6] In addition to this central role in energy production in the heart, mitochondria also perform a number of other essential functions in the heart, including roles in cal-

Abbreviations

CK/PCr: creatine kinase/phosphocreatine; **CPT:** carnitine palmitoyltransferase; **ETC:** electron transport chain; **GLUT:** glucose transporter; **MCT:** monocarboxylate transporter; **MPC:** mitochondrial pyruvate carrier; **MPTP:** mitochondrial permeability transition pore; **PDH:** pyruvate dehydrogenase; **ROS:** reactive oxygen species; **TCA:** tricarboxylic acid

cium homeostasis, ROS generation, and apoptotic signaling. As a result, situations where mitochondrial dysfunction occurs can have severe consequences on cardiac function, cardiac electrical activity, cardiomyocyte integrity, and cardiomyocyte survival.

Aging results in defects in cardiac mitochondrial function, which are the major reasons for the cellular and organ dysfunction that occurs with aging.[7] These defects include a decrease in cardiomyocyte mitochondrial volume, morphology, and respiration.[8] A key site of these mitochondrial defects is the electron transport chain, which is responsible for mitochondrial oxidative phosphorylation *(Figure 1)*. Mitochondrial defects in the electron transport chain occurs, in part, due to an age-related decrease in transcriptional and functional activity of the mitochondrial oxidative phosphorylation complexes.[7-10] This decrease in mitochondrial respiratory chain enzymes occurs to a larger extent in interfibrillar mitochondria vs subsarcolemmal mitochondria,[7] suggesting that aging compromises ATP supply to the cardiomyocyte contractile proteins. The expression and activity of complex III (cytochrome oxidase), complex IV, and complex V (ATP synthase) are particularly susceptible to aging, while complex I is relatively unaltered.[7,11] A decrease in cardiolipin, the key mitochondrial lipid, contributes to the decreased activity in complexes II-V.[12]

The mitochondrial electron transport chain is also a major site of ROS production in the heart. While the complexes I and III are major sites of ROS production, it is an aging-induced impairment of complex III that appears to be responsible for the increased cardiac ROS production seen with aging.[7,13] Impaired flux through the electron transport chain increases the direct interaction of the reduced redox centers with molecular oxygen to produce the free radical O_2^-, particularly in complex III. The increased ROS production in the aging heart can lead to oxidative damage in the mitochondria, including protein sulfhydryl oxidation, lipid peroxidation, and mitochondrial DNA damage. ROS also acts in mitochondrial metabolism–based stress signaling pathways, including the apoptotic pathway and the mitochondrial permeability transition pore (MPTP) opening. Increased mitochondrial ROS production increases apoptosis observed in the heart during aging.[7] Aging is also associated with an increase in the susceptibility of MPTP opening.[14] An increased ROS production with aging may contribute to this increased opening of the MPTP.[7] The opening of the MPTP can compromise mitochondrial function, increase mitochondrial calcium content, and alter membrane potential, and compromise cardiomyocyte function and survival.

Aging effects on myocardial energy production

Three potential effects of aging on myocardial energy production include: (i) a decreased capacity for energy production; (ii) alterations in fuel selection by the heart; and (iii) a decrease in energy transfer in the heart. These alterations in energy production, energy fuel selection, and energy transfer can negatively affect heart function and contribute to the development of heart failure in the aging heart.

Energy production capacity in the aging heart

The compromised cardiac mitochondrial integrity and the impairments in electron transport chain activity seen with aging are two important contributing factors to a decreased capacity for ATP production in the aging heart, which is associated with a decrease in high energy phosphate levels in the aging human heart.[15] In addition, the tricarboxylic acid cycle (TCA), which is critical for producing reduced equivalents necessary for the electron transport chain, also decreases with aging.[9] This decrease is partly due to a decrease in the expression of a number of genes of the TCA cycle.[10] As will be discussed, acetyl CoA supply to the TCA cycle is also compromised in the aging heart. Combined with the changes in the electron transport chain, mitochondrial oxidative capacity can drop by 50% in the human heart with aging.[16]

Energy substrate selection in the aging heart

Mitochondrial oxidative metabolism can use a variety of carbon substrates to produce the large amount of

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energy necessary to sustain contractile function, including the oxidation of fatty acids, pyruvate derived from glucose and lactate, ketones, and amino acids *(Figure 1)*.[6] The majority of cardiac mitochondrial ATP production originates from fatty acid oxidation, although pyruvate from glucose (glucose oxidation) can also be a significant source.[6] Normally, the heart maintains a high degree of metabolic flexibility, switching back and forth between different energy substrates to ensure an adequate energy production by the heart to meet the high energy demand of the heart. However, during aging, this metabolic flexibility is compromised. Unfortunately, there is no good consensus as to what actual switches occur in energy substrate metabolism. While it is generally thought that there is an impaired myocardial fatty acid oxidation and a compensatory increase in glucose metabolism (see reference 7 for a review of this subject), this is not supported by direct measurements of energy substrate flux. Direct measurements of energy substrate metabolism in the heart showed an increase in fatty acid oxidation in aged rats compared with young rats, with a parallel decrease in carbohydrate oxidation.[17] This finding is supported by measurements of gene profiles in hearts of aging humans, in which an increase in fatty acid oxidation genes and a decrease in pyruvate dehydrogenase (the rate-limiting enzyme for glucose and lactate oxidation) was observed.[10] It should be noted, however, that aging-induced increases in pyruvate dehydrogenase have also been observed in the rat heart.[18] As a result, further studies are needed to have a better understanding of what changes in fuel selection occur in the aging heart. It should be noted that inhibition of fatty acid oxidation in the skeletal muscle of aging mice improves glucose and insulin tolerance and protects

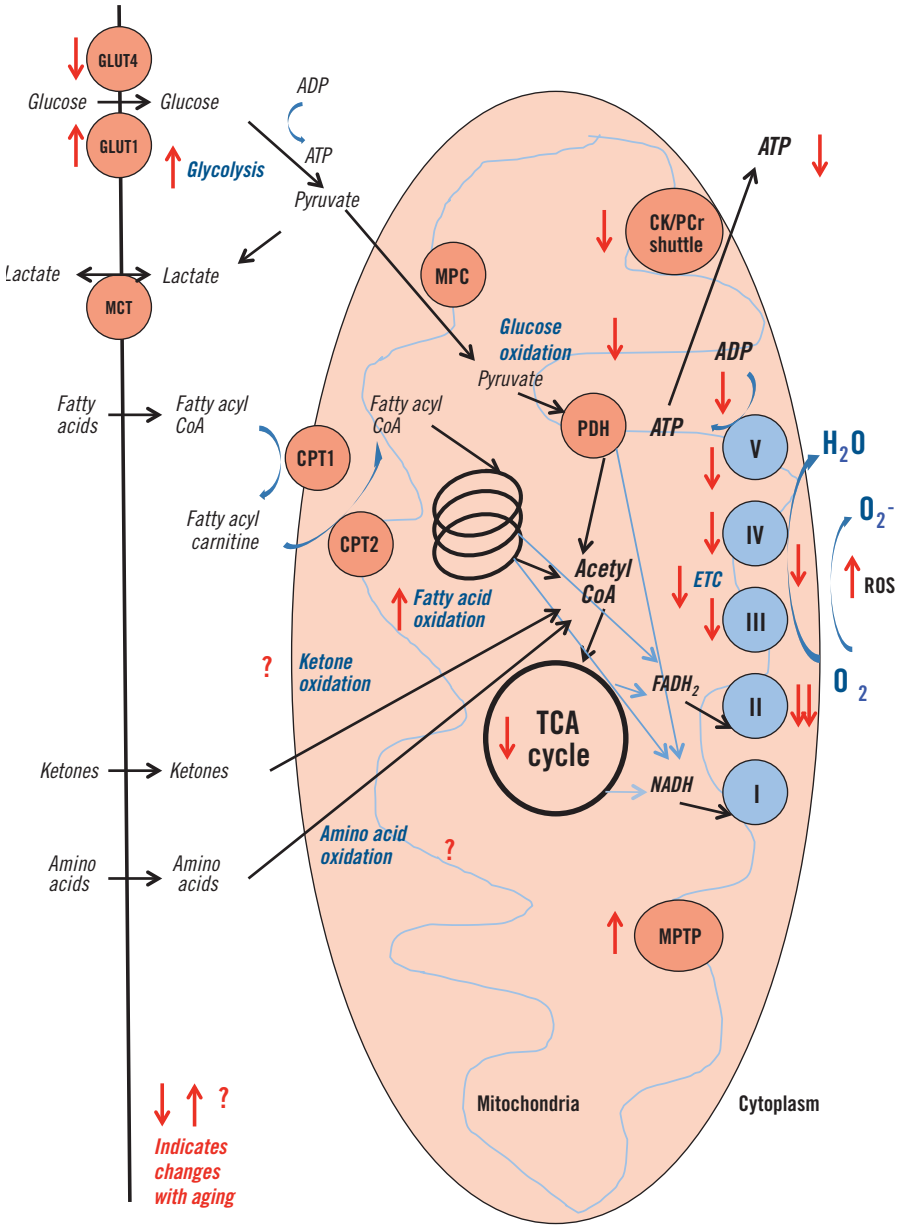

Fig. 1 *Alterations in myocardial energy metabolism in the aged heart. In the aerobic heart, mitochondrial fatty acid oxidation and glucose oxidation are the major sources of energy production in the heart. In the aging heart, both mitochondrial ETC activity and TCA cycle activity are compromised, leading to an impaired production of ATP from oxidative metabolism. Impaired ETC activity can also increase ROS production in the aging heart. The aging heart also becomes "metabolically inflexible" with fatty acid oxidation increasing at the expense of glucose oxidation, a situation that can decrease cardiac efficiency. Glycolysis increases in the aging heart in an attempt to increase ATP production, although this increase in glycolytic ATP production cannot compensate for the loss of mitochondrial ATP production, leaving the heart in a potentially "energy starved" situation.*
Abbreviations: *CK/PCr, creatine kinase/phosphocreatine; CPT, carnitine palmitoyltransferase; ETC, electron transport chain; GLUT, glucose transporter; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier; MPTP, mitochondrial permeability transition pore; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; TCA, tricarboxylic acid.*

against age-related metabolic dysfunction.[19] Whether a similar approach may also be beneficial in the aging human heart has yet to be determined.

With a decrease in mitochondrial oxidative capacity and possible decreases in fatty acid and carbohydrate oxidation, the aging heart can become "energy starved," particularly during times of stress or increased energy demand. One attempt to counter this decrease in mitochondrial ATP production is to increase glycolytic ATP production. An increase in the reliance on glycolysis as a source of ATP production has been shown in aging rats and humans.[20,21] However, the amount of ATP produced from glycolysis is small compared with the amount of mitochondrial ATP produced, leaving the potential for the aging heart to remain in an energy compromised state.

Energy transfer in the aging heart

Transfer of mitochondrial produced ATP to its site of use in the cytoplasm requires a creatine kinase (CK)/phosphocreatine (PCr) shuttle pathway *(Figure 1)*. To date, there is no clear consensus as to whether this energy transfer is compromised with aging. Studies have shown no change, an increase, or a decrease in the CK/PCr pathway (see reference 5 for a review of this topic). While decreases in PCr have been observed in aging humans,[22] it is not clear if this is due to alterations in the actual energy transfer process or a decrease in the actual mitochondrial energy production, resulting in a decreased transfer of high energy phosphates from ATP to PCr. While studies have attempted to improve cardiac energetics in the aging heart by altering the CK/PCr shuttle, the results of these studies have not been encouraging.

Conclusions

Aging leads to defects in mitochondrial energy production in the heart, due, in large part, to decreased mitochondrial integrity and decreased activity of the electron transport chain and TCA cycle. Alterations in energy substrate selection contribute to a metabolic inflexibility in the aging heart that may decrease the ability of the heart to deal with pathological stress and increased energy demands, which raises the possibility that therapeutic strategies to improve mitochondrial energy production and metabolic flexibility may be an approach to improve cardiac function in the elderly population. ■

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