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Abstract

Energy metabolism is at the crossroad of cell function and dysfunction. Cardiac and skeletal muscle cells whose energy metabolism is high, fluctuating and adaptable to the special needs of the body have developed sophisticated strategies for synthesizing, transferring and utilizing energy in accordance with the needs of the body. Adaptation to endurance training mainly involves energetic remodelling in skeletal muscle but less is known for the cardiac muscle. Alterations in energy metabolism participate in many pathophysiological processes among which heart failure. Because endurance training improves symptoms and quality of life and decreases mortality rate and hospitalization, it is increasingly recognized as a beneficial practice for heart failure patients. The mechanisms involved in the beneficial effects of exercise training are far from being understood. Proper evaluation of these mechanisms is thus a major health issue for populations leaving in industrialized countries. This review mainly focuses on oxidative metabolism and intracellular energy transfer in muscles and heart, their alterations in heart failure and effects of endurance exercise training.

Cardiac and skeletal muscle energy metabolism

It has long been known that the energetic characteristics of muscle cells are not uniform but adapted to the specific requirements of a given muscle. Schematically, two extreme metabolic patterns have been defined. Fast skeletal muscle fibers mainly rely on quickly mobilisable energy sources to develop strong and fast contractions but this is possible only for short periods of time because of limited cellular metabolic reserves (mainly phosphocreatine (PCr) and glycogen). These muscles are quickly fatigable and exhibit delayed recovery of their energy reserves through anaerobic glycolysis and less importantly mitochondrial oxidations. Slow muscles, on the contrary develop lower contractile force but are able to maintain longterm contractile activity because they rely on oxidative phosphorylations. They should have accurate adjustment of energy production to energy consumption. Creatine kinase (CK) and other phosphotransfer kinases (like myokinase) participate in energy shuttling within cardiac and skeletal muscle cells (reviewed in (Ventura-Clapier et al. 1998;Saks et al. 2006)). CK isoenzymes are located on sites of energy production (mitochondria or glycolytic complexes) and utilization (myosin and sarcoplasmic reticulum ATPases), ensuring fast and efficient energy transfer to ATPases, and signal transfer to energy producing sites. Mitochondria can themselves directly support myofibrillar/SR-calcium ATPase function as efficiently as the bound CK system, and much better than cytosolic ATP alone (Kaasik et al. 2001;Saks et al. 2001). This indicates that a localized crosstalk between energy producing and energy consuming sites in the cardiac cell is required to ensure proper cardiac contractility. This finetuning of energy fluxes in oxidative muscle and heart underlies fatigue resistance. The setting of muscle type specific oxidative capacity is linked to the process of mitochondrial biogenesis and the role of the mitochondrial biogenesis transcription cascade, in which the transcriptional co-activator PGC-1α play a major role (Ventura-Clapier et al. 2008).

Effects of exercise training

Endurance training improves cardiovascular and muscle function. It is now accepted that an important component of the effects of exercise training involves modifications of skeletal muscle energy metabolism, and that these effects participate in the beneficial effects of training. Adaptive responses of the heart to endurance training include resting and submaximal exercise bradycardia and increase in end-diastolic dimension. This leads to nonpathological cardiac hypertrophy, improved ventricular function and increase in the resistance of the heart to ischemic insult (Moore 1998). However, whether changes in energy production and transfer occur to preserve or improve cardiac function is still unclear.

Results from animal models have shown that regular exercise increases glycolysis and oxidative metabolism while other studies favored an increase in muscle mass rather than in mitochondrial gene expression (Stuewe et al. 2000; Coleman et al. 1988; Murakami et al. 1995; Kayar et al. 1986), and involved an increased protection against aging-induced increase in oxidative stress (Rosa et al. 2005;Marcil et al. 2005). Moreover, either increase or no change in fatty acid utilization capacity were reported (Terblanche et al. 2001; Iemitsu et al. 2003). Little is known concerning creatine kinase expression and function in trained heart. Aerobic exercise training increases total myocardial CK activity and MB-CK content in canine left ventricular myocardium (Stuewe et al. 2001) but the physiological relevance of this observation is not obvious. Thus whether the heart adapts to repeated exercise by improving energy synthesis and energy fluxes or both await further investigation. Whether these results extend to human heart remains to be established.

Skeletal muscles adapt to repeated prolonged exercise by marked quantitative and qualitative changes in mitochondria, capillary supply, but only limited transitions in MHC isoforms (Fluck and Hoppeler 2003; Koulmann and Bigard 2006; Hood et al. 2006).

Endurance training promotes an increase in mitochondrial volume density and mitochondrial proteins, in all fiber types (Howald et al. 1985) together with an increased efficacy of energy transfer (Zoll et al. 2002; Zoll et al. 2003). PGC-1α expression plays a key role in regulating mitochondrial biogenesis in skeletal muscle during endurance training, and correlates with the training status of healthy individuals (Garnier et al. 2005).

Energy metabolism in heart failure

The energetic failure of the failing heart includes 1) an early switch in substrate utilization from fatty acid to glucose, 2) a decreased oxidative capacity and energy production due to decreased mitochondrial biogenesis, 3) a decreased energy transfer by the phosphotransfer kinases, 4) an altered energy utilization and finally 5) a decreased efficiency of energy consumption. It was shown recently that the decreased cardiac muscle oxidative capacity in heart failure is associated with the down-regulation of PGC-1α, and its downstream transcription cascade (Garnier et al. 2003), and extended to other models of heart failure (Zoll et al. 2006; Kemi et al. 2007; Sun et al. 2007 ; Javadov et al. 2006; Watson et al. 2007) and to the human failing heart (Sebastiani et al. 2007). This suggests that the decreased expression of the PGC-1α/PPARα transcription cascade is the molecular basis for energy starvation of the failing myocardium (Neubauer 2007).

In animal models, the decreased oxidative capacity of skeletal muscles in heart failure is linked to the down regulation of the mitochondrial biogenesis transcription cascade (Garnier et al. 2003). Metabolic alterations in heart failure affect both cardiac and skeletal muscles, suggesting a generalized metabolic myopathy in this disease (Ventura-Clapier et al. 2002). Impairment in skeletal muscle mitochondrial function in patients deserves further considerations. Changes in skeletal muscle morphology, metabolism and function in CHF patients include muscle atrophy, decreased vascularisation, fiber type shift towards faster phenotype, and decreased resistance to fatigue (Drexler and Coats 1996). Recent studies have demonstrated however that in situ muscle oxidative capacity, mitochondrial ATP production and the transcriptional cascade PGC-1/NRFs/Tfam is identical in CHF patients and sedentary subjects (Mettauer et al. 2001; Williams et al. 2004; Garnier et al. 2005). One possible explanation is a beneficial effect of recent HF therapy (Zoll et al. 2006). Nevertheless, defects in creatine kinase and citrate synthase activity (Mettauer et al. 2001) are still observed suggesting persisting metabolic defects in skeletal muscle in CHF patients.

Beneficial effects of exercise training in heart failure

Endurance training improves muscle resistance to fatigue and exercise training is able to oppose the deleterious effects of heart failure on skeletal muscle energy metabolism, although this is less clear for cardiac muscle. Although some observations indirectly suggest that exercise training can improve myocardial energy metabolism (Gielen et al. 2001; Wang et al. 1997), direct evidences for beneficial effects of exercise training on cardiac energy metabolism are sparse. Recent studies have established that in experimental heart failure, exercise training restores cardiac energy metabolism partially by improving oxidative capacity and restoring deficiency in energy transfer (Kemi et al. 2007).

Effects of exercise training on skeletal muscle of CHF patients are more documented. In chronic heart failure patients, endurance training reduces phosphocreatine depletion and ADP increase during exercise, and enhances the rate of phosphocreatine resynthesis after exercise indicating a substantial improvement of skeletal muscle oxidative capacity (Adamopoulos et al. 1993). Increase in mitochondrial volume density positively correlates with changes in VO_2 peak and anaerobic threshold exercise (Hambrecht et al. 1995). Whether this increase in mitochondrial density and oxidative capacity with training in CHF occurs because of increased coordinated transcription of nuclear and mitochondrial genes is presently undemonstrated. However, this hypothesis is likely because of the coordinated changes in PGC-1α expression, muscle oxidative capacity, VO_2 peak and the training status in healthy individuals and in CHF patients (Garnier et al. 2005). Interestingly, a strong correlation can be established between expression of mitochondrial and cytosolic creatine kinase isoenzymes and exercise capacity (Kemi et al. 2007). Nevertheless, direct assessment of the beneficial effects of exercise training on mitochondrial function and energy transfer in heart failure still deserve further considerations.

Conclusion

Heart failure induces a metabolic myopathy affecting both heart and skeletal muscles. This mainly involves decreased oxidative capacity, shift in substrate utilization and altered energy transfer by phosphotransfer kinases. In skeletal muscle, endurance exercise capacity is mainly conditioned by increased oxidative capacity, and improvement of energy fluxes and better coupling between energy production and utilization. Prolonged exercise is thus able to counteract these deleterious effects by improving oxygen and substrate delivery, as well as metabolic remodeling of cardiac and skeletal muscles. Although beneficial effects of endurance training in heart failure are indubitable, further work is needed to delineate the pleiotropic effects of physical activity on cardiac and skeletal muscle functions. This issue is of interest for clinical output, especially for rehabilitation of patients with heart failure.

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