Pharmacological Research 115 (2017) 96–106

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Disruption of mitochondrial quality control in peripheral artery disease: New therapeutic opportunities

Cintia B. Ueta[a,1], Katia S. Gomes[a,1], Márcio A. Ribeiro[a,1], Daria Mochly-Rosen[b], Julio C.B. Ferreira[a,*]

[a] Department of Anatomy, Institute of Biomedical Sciences, University of São Paulo, Brazil
[b] Department of Chemical and Systems Biology, Stanford University School of Medicine, USA

ARTICLE INFO

Article history:
Received 11 July 2016
Received in revised form
10 November 2016
Accepted 12 November 2016
Available online 19 November 2016

Keywords:
Myocyte
Mitochondrial metabolism
Redox balance
4-Hydroxynonenal
Mitochondrial dynamics
Mitophagy

ABSTRACT

Peripheral artery disease (PAD) is a multifactorial disease initially triggered by reduced blood supply to the lower extremities due to atherosclerotic obstructions. It is considered a major public health problem worldwide, affecting over 200 million people. Management of PAD includes smoking cessation, exercise, statin therapy, antiplatelet therapy, antihypertensive therapy and surgical intervention. Although these pharmacological and non-pharmacological interventions usually increases blood flow to the ischemic limb, morbidity and mortality associated with PAD continue to increase. This scenario raises new fundamental questions regarding the contribution of intrinsic metabolic changes in the distal affected skeletal muscle to the progression of PAD. Recent evidence suggests that disruption of skeletal muscle mitochondrial quality control triggered by intermittent ischemia-reperfusion injury is associated with increased morbidity in individuals with PAD. The mitochondrial quality control machinery relies on surveillance systems that help maintaining mitochondrial homeostasis upon stress. In this review, we describe some of the most critical mechanisms responsible for the impaired skeletal muscle mitochondrial quality control in PAD. We also discuss recent findings on the central role of mitochondrial bioenergetics and quality control mechanisms including mitochondrial fusion-fission balance, turnover, oxidative stress and aldehyde metabolism in the pathophysiology of PAD, and highlight their potential as therapeutic targets.

Contents

1. Introduction

Peripheral artery disease (PAD) is a manifestation of atherosclerosis that results in either partial or complete obstruction of the peripheral arteries with consequent reduction of blood flow to the affected limb. PAD affects approximately 10% of individuals over

* Corresponding author at: Departamento de Anatomia, Instituto de Ciências Biomédicas da Universidade de São Paulo, Av. Professor Lineu Prestes, 2415, São Paulo, SP, CEP 05508-000–Brazil.
E-mail address: jcesarbf@usp.br (J.C.B. Ferreira).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.phrs.2016.11.016
1043-6618/

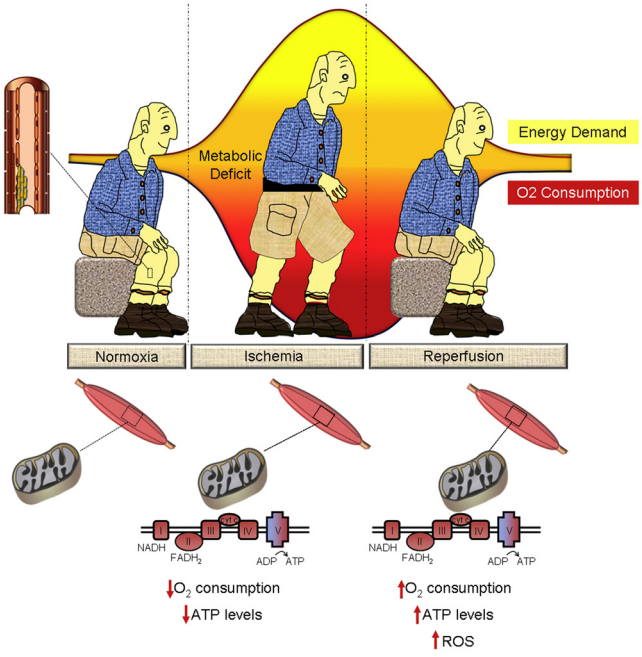

Fig. 1. Schematic panel showing the process of ischemia-reperfusion injury triggered by exercise-rest cycles in PAD patients with intermittent claudication. During exercise, there is an increased skeletal muscle energy demand. However, limited limb energy transferring due to impaired blood flow and mitochondrial dysfunction causes a metabolic deficit and consequent exercise cessation. After cessation of exercise [and consequent reperfusion of the ischemic limb] mitochondria-mediated energy transferring is reestablished. However, intrinsic changes occurred during repeated cycles of ischemia-reperfusion injury cause mitochondrial dysfunction and accumulation of reactive oxygen species, therefore, contributing to a progressive metabolic deficit and skeletal muscle degereration in PAD.

the age of 65 years, and about 20% of individuals over the age of 80 years [1].

PAD has become a global burden in the 21 st century. The number of individuals with PAD increased about 21% during the last decade, affecting over 200 million people in both high-income countries and low-to-middle-income countries [2]. Therefore, PAD is considered one of the most harmful and morbid noncomunicable diseases worldwide. Its progression, initially triggered by reduced blood supply to lower extremities, is associated with myopathy, exercise intolerance and to limb amputation in most the extreme cases. PAD causes a pronounced reduction in both exercise performance and routinely ambulatory activities, thus causing a major decline in quality of life [3,4]. In addition to its direct effect on the ischemic limbs, PAD has a detrimental impact on the cardiovascular system; individuals with PAD have increased risk of cardiovascular events, cardiovascular disease mortality and all-cause mortality compared to the general population [5]. Indeed, it is expected that about 22% of PAD patients will die from coronary or cerebrovascular disease during a 10 year period [6].

2. Diagnosis and classification

Despite of its epidemological relevance as well as its negative impact in quality of life due to elevated rates of limb-related morbidity and cardiovascular events, PAD is considered an unmet clinical need. Unfortunately, most of individuals with PAD are not diagnosed accordingly in primary care practice [7,8].

PAD can be classified into 4 categories according to symptoms: asymptomatic, atypical leg symptoms associated with exercise intolerance, intermittent claudication and critical limb-ischemia. Diagnosis of PAD is focused primarily on classical intermittent claudication symptoms, characterized by exercise-induced leg pain that is relieved by rest. Intermittent claudicaton can be detected by performing a 6-min walk test [9] or applying different surveys such as the self-reported Walking Impairment Questionnaire or the Rose Claudication Questionnaire [10]. These methods are highly sensitive in detecting intermittent claudication, the most typical symptom of PAD. However, only about 20% of individuals with PAD have signs of intermittent claudication [8]. Aproximately 50% of people with PAD are asymptomatic and about 30% have exertional leg symptoms other than intermitent claudication [8,11,12]. Therefore, other methods to detect PAD are required to overcome the frequent underdiagnosis of PAD.

PAD can be noninvasively identified in primary care practice using the ankle-brachial index (ABI), which is the ratio of Doppler recorded systolic blood pressure at the ankle to that in the arm [13,14]. It is considered a simple, accurate and reproducible test, presenting high sensitivity and specificity as compared to other methods [15]. PAD is defined by ABI $\leq$0.9 [14,16,17]. Recently, the American Heart Association (AHA) guidelines recommended that borderline ABI rate between 0.91 and 0.99 should be classified as mild stenosis [17].

In general, the definition of symptomatic PAD relies on the presence of both typical intermitent claudication and abnormal ABI (<0.90), where asymptomatic PAD is characterized by abnormal ABI alone without limb symptoms. However, most medical practices do not routinely measure ABI. A recently published systematic review on the diagnostic and prognostic value of the ABI concluded that there is insufficient evidence supporting the accuracy of ABI as a screening tool [18]. Therefore, detecting PAD in either asymptomatic individuals or those who have atypical leg symptoms remains challenging.

3. Mechanisms

There are convincing evidence supporting the primary pathophysiology of PAD, initially triggered by an atherosclerotic obstruction of the lower extremities with consequent decrease in blood flow (ABI < 0.9). In fact, increasing blood supply to the compromised limb after surgical revascularization clearly improves symptoms and hemodynamic parameters in PAD patients with lifestyle limiting claudication or critical limb ischemia [19]. However, this procedure is not sufficient to induce recovery of metabolic properties and functional capacity [20,21].

PAD progression cannot be solely explained by reduced blood flow to the affected limb [22]. In fact, a decline in ABI values does not necessarily reflect a worsen PAD clinical outcome [19,23]. Pipinos et al. have provided evidence using magnetic resonance spectroscopy that PAD patients with mild to moderate claudication have lower extremity dysfunctional energy metabolism independent of both blood flow and severity of vascular occlusion [24]. Moreover, McDermott et al. demonstrated that PAD patients with similar hemodynamic dysfunction (similar ABI values) have different symptoms ranging from asymptomatic to intermittent claudication [25]. Therefore, additional mechanisms rather than impaired hemodynamics might contribute to PAD pathophysiology.

Recent evidence suggests that PAD-related morbidity depends on changes in metabolic, morphologic and functional status of the skeletal muscle distal to the primary arterial obstruction [7,22,26,27]. Lower extremity skeletal muscles of patients with PAD present dysfunctional bioenergetics, increased fat deposition, sarcopenia, loss of strength and impaired contractility properties as compared with skeletal muscles of individuals without PAD [25,26,28–30]. Mc Dermott et al. found that ABI values positively correlate with skeletal muscle cross-sectional area [31]. Of interest, the same group demonstrated in another study that PAD