Free Radical Biology and Medicine 98 (2016) 13–17

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Cellular mechanisms underlying oxidative stress in human exercise

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ARTICLE INFO

Article history:
Received 29 November 2015
Received in revised form
16 February 2016
Accepted 17 February 2016
Available online 18 February 2016

ABSTRACT

A relative increase in oxidation of lipids, proteins and DNA has been recognised to occur in the circulation and tissues of exercising humans and animals since the late 1970s and throughout the ensuing 40 years a great deal of work has been undertaken to elucidate the potential source(s) of this exercise-induced "oxidative stress". Specific aspects of physical exercise (e.g. contractile activity, relative hypoxia, hyperaemia) may theoretically induce increased generation of reactive oxygen species in a number of potential tissues, but data strongly indicate that contractile activity of skeletal muscle predominates as the source of oxidants and contributes to local oxidation and that of extracellular biomaterials. Taken together with the relatively large mass of muscle compared with other tissues and cells it appears that muscle fibres are the major contributor to the relative increase in whole body "oxidative stress" during some forms of exercise. The sub-cellular sources of this increased oxidation have also been the subject of considerable research with early studies predominantly indicating that muscle mitochondria were the likely increased source of oxidants, such as hydrogen peroxide, but assessments of the relative concentrations of hydrogen peroxide in skeletal muscle fibres at rest and during contractile activity do not support this possibility. In contrast, several recent studies have identified NADPH oxidase enzymes in skeletal muscle that appear to play a signalling role in physiological responses exercise and together with xanthine oxidase enzymes may contribute to the relative increase in whole body oxidation. A fuller understanding of the relative roles of these sources and the function(s) of the species generated appears increasingly important in attempts to harness the beneficial effects of exercise for maintenance of health in aging and a variety of chronic conditions.

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1. Introduction

The first concerted studies of the generation and potential roles of free radicals and reactive oxygen species (ROS) during exercise date from the late 1970s and early 1980s [e.g. 1–3] and during the ensuing years a great deal of research has been undertaken to try and understand the sources and identity of the species generated, the factors influencing their generation, their biological effects and how these effects might be manipulated. An assumption that underpinned much of the initial work was that the species generated caused oxidative stress and were deleterious to cells and tissues, and even the earliest studies attempted to scavenge the species generated and look for potential functional benefits of the intervention [1]. These early studies were also characterized by limitations in the analytical techniques and approaches available and now outmoded approaches such as the analysis of volatile hydrocarbons in breath or TBARS in complex biological tissues were commonly used.

The likely tissue source(s) of the increased levels of markers of oxidative stress detected in the circulation during exercise have received relatively little attention although there has been a general assumption that contracting skeletal muscle was a major source for the generation of free radicals/ROS during exercise. Davies et al. [2] pointed out the potential role of mitochondria in heart and skeletal muscle as a source of these species, while Jackson et al. [3] demonstrated an increase in free radical generation in contracting skeletal muscle using electron paramagnetic resonance techniques, but other possible sources including respiring lung tissue, vascular tissue and immune cells have all been implicated as contributors to the oxidative stress that has been reported during exercise (see [4] for review). A recent paper has also critically examined the way that relevant environmental (hyperthermia or dehydration) and physiological changes (osmotic stress) can impact on exercise-induced ROS generation [5] and readers interested in this area are urged to consult this review.

The aims of this review are to briefly summarise current knowledge concerning major sources of ROS generation during exercise at tissue, cell and sub-cellular levels in order to aid

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http://dx.doi.org/10.1016/j.freeradbiomed.2016.02.023
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understanding and regulation of these species, topics that are addressed in other reviews in this series.

2. Demonstration that contracting skeletal muscle can cause a systemic oxidative stress

Although it was recognised at a relatively early stage that contractile activity could lead to generation of free radicals and ROS in skeletal muscle tissue [3], the potential of this to lead to oxidation in other tissues or circulating molecules outside of the muscle was not recognised until Michael Reid and colleagues [6] identified the release of a specific reactive oxygen species (superoxide) from strips of diaphragm ex vivo. This observation raised the possibility that contracting muscle tissue might provide a source of ROS that could influence other tissues and lead to oxidation of lipids, DNA or proteins (i.e. markers of oxidative stress) in the circulation. Subsequently O'Neill et al. [7] directly sampled the venous outflow from the *triceps surae* muscle of anesthetised cats and demonstrated an increase in hydroxyl radical activity in response to muscle contractions induced by stimulation of the sciatic nerve. This appears to be the first paper to demonstrate the capacity of contracting skeletal muscle tissue to influence oxidation in other tissues or blood components by inducing oxidation of extracellular compounds (in this case phenylalanine perfused as a probe to detect hydroxyl radicals). Indirect evidence for such effects was also supplied by others, including Close et al. [8], who showed that contraction of the hind limb muscles of anaesthetised adult mice induced by direct electrical muscle stimulation and not associated with any whole body exercise caused transient, but significant increases in the serum and liver malonaldehyde content and a decrease in liver glutathione and protein thiol content (Fig. 1). Thus collectively these and other data indicate that contracting skeletal muscle generates reactive oxygen species that can oxidise extracellular molecules and lead to an increase in oxidative stress markers in other tissues and the circulation. Within the muscle tissue being sampled there are various potential cell types (e.g. skeletal muscle fibres, various vascular cells, endothelial cells, blood cells) that may contribute to the ROS generated. It also remains unclear whether tissues other than muscle (e.g. lung or liver) that become more metabolically active during exercise share this capacity to contribute to the increase in whole body measures of oxidative stress, but the large proportion of body mass that is constituted by skeletal muscle suggests that this tissue must represent at least one of the major sources of ROS contributing to oxidative stress during exercise.

Similar data from human studies that demonstrate a role for skeletal muscle in causing whole body effects on oxidation have been difficult to obtain, but a recent paper by Nyberg et al. [9] goes some way to address this. These investigators examined the effects of acute exercise on changes in blood redox state across the leg of young and older humans by measuring the whole blood concentrations of reduced (GSH) and oxidised (GSSG) forms of glutathione. They observed that exercise increased the venous concentration of GSSG in an intensity dependent manner which they ascribed to an exercise-induced increase in ROS formation by muscle tissue (Fig. 2).

Although these data indicate a likely substantial role for contracting skeletal muscle in inducing a whole body oxidative stress in mice and humans, it is noteworthy that the data in Figs. 1 and 2 both show this effect is limited to adult mice and young human subjects, while older mice and humans do not show the same responses to exercise. A full description of this modified response with ageing is beyond the remit of this review, but readers are referred to Jackson and McArdle [10] and Palomero et al. [11] for a fuller discussion of this area.

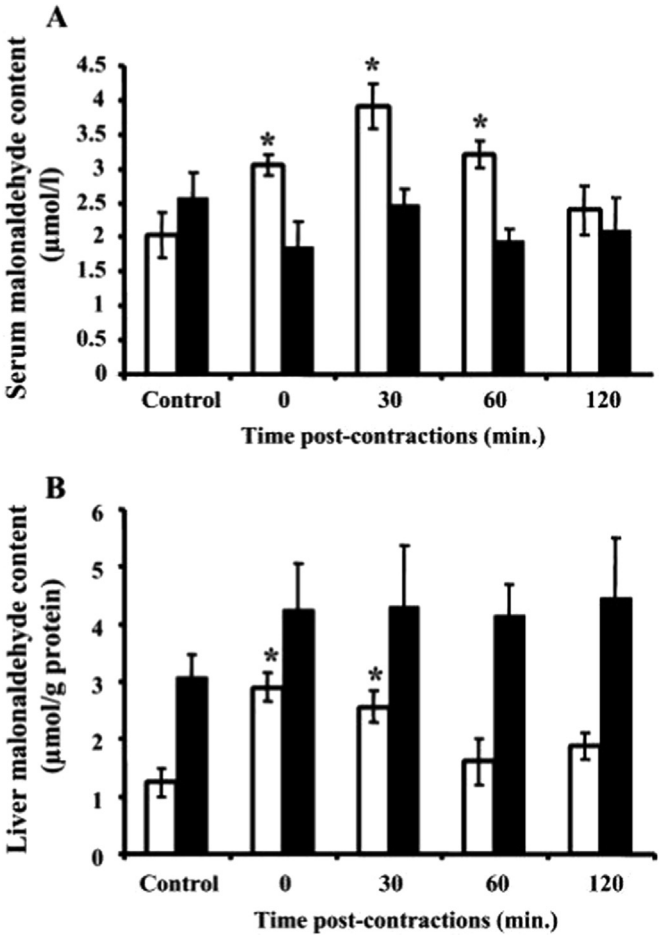

Fig. 1. (A) Serum malonaldehyde (MDA) concentration for adult (open bars) and old (black bars) mice that were not stimulated (control), and mice immediately post-contractions (0 time), 0.5 h post-contractions, 1 h post-contractions, and 2 h post-contractions. Serum MDA concentration was increased above control values immediately, 30 and 60 min postcontractions (*$P < 0.05$ compared with pre-contractions values). (B) Liver MDA content for adult (open bars) and old (black bars) mice that were not stimulated (control) and mice immediately post-contractions (0 time), 0.5 h post-contractions, 1 h post-contractions, and 2 h post-contractions. MDA content was increased above control values immediately and 30 min postcontractions. *$P < 0.05$ compared with control values. Data from Close et al. [8].

3. Which cell type within the muscle tissue is important in generation of reactive oxygen species?

The muscle tissue from which the venous eluent was sampled to provide the data in Fig. 2 contains a variety of cell types that might potentially contribute to ROS generation during contractions including vascular smooth muscle cells, endothelial cells, fibroblasts, erythrocytes and white blood cells in addition to skeletal muscle fibres. Although multiple cell types are present, the relatively high proportion of the tissue that is composed of muscle fibres compared with other cell types suggests that muscle fibres are likely the major contributors to exercise-induced ROS generation, and studies of myotubes [12,13] and isolated mature muscle fibres in culture [e.g. 11] indicate the substantial potential of pure skeletal muscle cells/fibres to release ROS or generate ROS on their extracellular surface. Some data do support a role for an alternative cell type, endothelial cells, in ROS generation in muscle tissue since inhibitor studies suggest that xanthine oxidase enzymes may contribute to ROS release from muscle during contractile activity [14]. Skeletal muscle cells do not appear to contain

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