Redox Biology 35 (2020) 101484

Contents lists available at ScienceDirect

Redox Biology

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

Hydrogen peroxide as a signal for skeletal muscle adaptations to exercise: What do concentrations tell us about potential mechanisms?

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A B S T R A C T

Hydrogen peroxide appears to be the key reactive oxygen species involved in redox signalling, but comparisons of the low concentrations of hydrogen peroxide that are calculated to exist within cells with those previously shown to activate common signalling events *in vitro* indicate that direct oxidation of key thiol groups on "redox-sensitive" signalling proteins is unlikely to occur. A number of potential mechanisms have been proposed to explain how cells overcome this block to hydrogen peroxide-stimulated redox signalling and these will be discussed in the context of the redox-stimulation of specific adaptations of skeletal muscle to contractile activity and exercise. It is argued that current data implicate a role for currently unidentified effector molecules (likely to be highly reactive peroxidases) in propagation of the redox signal from sites of hydrogen peroxide generation to common adaptive signalling pathways.

1. Introduction

A number of observations indicate that reactive oxygen species (ROS) play a role as stimulants of beneficial adaptations to contractile activity in skeletal muscle. The key molecule involved in this redox stimulation appears to be hydrogen peroxide (H_2O_2), but it is unclear how the H_2O_2 can activate the necessary signalling pathways that facilitate functional adaptations to contractile activity. In this brief review we will examine the extent of the beneficial adaptations to contractions that may be stimulated by H_2O_2, identify several key cell signalling pathways that may be involved in the responses and describe the quantitative discrepancies which reduce confidence in the potential role of H_2O_2 in these processes. Potential mechanisms that may overcome these discrepancies will also be described.

2. Exercise induces multiple adaptations in contracting skeletal muscle

Skeletal muscle adapts to different forms of exercise in many positive ways including an increase in aerobic capacity, increased muscle force generation, increased mass and decreased fatigability. The mechanisms underlying these processes have been the subject of a number of studies and key pathways have been identified that provide potential targets for interventions aimed at optimising the beneficial effects of exercise [1]. Despite these substantial developments there is still a lack of understanding of the specific changes that occur in muscle during exercise to trigger the signalling pathways leading to these adaptations. Reactive oxygen species (ROS), specifically hydrogen peroxide (H_2O_2), have been proposed as one of the key factors that stimulate adaptive changes in contracting skeletal muscle [2–4].

3. Inhibitor studies indicate that the range of adaptations to exercise stimulated by H_2O_2 is extensive

Muscle fibres respond to contractile activity by an increase in the intracellular generation of superoxide and nitric oxide (NO) with the formation of secondary ROS and reactive nitrogen species [2,5,6]. Although ROS were initially reported to be inevitably deleterious to cells causing oxidative damage to lipids, DNA and proteins [7,8], their role as important physiological signalling molecules with regulatory functions that modulate changes in cell and tissue homeostasis and gene expression has become increasingly apparent [9–11]. Signalling by these reactive molecules is mainly achieved by targeted redox modifications of specific residues in proteins [12,13].

Many original studies of ROS generated in muscle during exercise were predicated on an assumption that these species were deleterious and that administration of supplementary antioxidants would be beneficial (e.g. Refs. [14,15]). Thus, studies examined the effects of high doses of single antioxidant nutrients, or mixtures of these in rodents and humans undertaking various exercise protocols. The data obtained were variable, but many of these studies demonstrated that antioxidants inhibited cytoprotective responses, such as the increase in heat shock and other stress proteins [16,17] that followed exercise, inhibited mitochondrial biogenesis [18–20], prevented the beneficial increase in

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https://doi.org/10.1016/j.redox.2020.101484
Received 22 January 2020; Received in revised form 24 February 2020; Accepted 28 February 2020
Available online 29 February 2020

muscle insulin sensitivity [18] and inhibited the release of cytokines and inflammatory mediators [21]. The apparent lack of consistency in outcomes from these studies prompted considerable discussion in the scientific literature [22,23], but overall these data support the possibility that ROS act as beneficial signalling molecules that mediate multiple adaptations to exercise.

4. Key signalling pathways involved in muscle adaptations have been proposed to be redox regulated

Studies have identified several key signalling pathways involved in skeletal muscle responses to contractile activity for which there is evidence that redox regulation is important, although the exact mechanisms and proteins involved remain unclear. We discuss briefly below four key signalling pathways which are activated in muscle by contractile activity and which are likely to play a role in the functional changes following exercise which are inhibited by antioxidants as reported above (i.e. the increase in muscle cytoprotective heat shock proteins [16] and other stress responses [17], increased mitochondrial biogenesis [18–20], muscle insulin sensitivity [18] and release of cytokines and inflammatory mediators [21]) and which have some evidence of redox regulation. The four pathways are:

1. ***Mitogen-activated protein kinases (MAPK).***

This group of kinases includes p38-MAPK and JNK which are both involved in many stress responses and are activated in skeletal muscle by contractile activity [24]. Both kinases are activated by high micromolar levels of H_2O_2 in cell culture and regulation by oxidation has been demonstrated at multiple points in the signalling pathway (see Ref. [25] for a brief review). Activation of both p38-MAPK and JNK signalling cascades is triggered by a group of proteins termed the MAPK kinase kinases (MAP3K), which become phosphorylated and activated in response to a diverse range of stimuli. Upon their activation MAP3Ks can phosphorylate and activate intermediary MAP2K proteins such as MEK3 and MEK6, (which go on to phosphorylate p38-MAPK) or MEK4 and MEK7 (which target JNK). A number of key proteins in the pathway have been identified where oxidation can activate the pathway, but it is currently unclear whether H_2O_2 acts directly on these proteins or via intermediary redox-sensitive protein(s). For example, ASK1 (a MAP3K) has recently been demonstrated to bind to, and become oxidised by Prx during increased oxidative stress in cells [26]. These data support the hypothesis that the effects of increased oxidation during contraction-induced muscle cell signalling pathways may be mediated by Prx which is discussed later. An analogous association between Prx and a second MAP3K, MEKK4, has also been observed [27]. Exposure of cells to H_2O_2 has also been shown to induce interactions between p38-MAPK and MEK3 via disulphide bridge formation [25], although again it is unclear whether H_2O_2 oxidises these proteins directly or via intermediary redox-sensitive proteins.

2. ***Protein tyrosine phosphatases (PTP).***

These are a key group of enzymes that dephosphorylate multiple signalling proteins including those involved in the regulation of muscle glucose uptake and insulin sensitivity [28]. Insulin-induced glucose uptake is mediated by a pathway initiated at the muscle cell surface by the insulin receptor and its associated proteins IRS1 and PI3K. Activation of these lead to an accumulation of PIP3 at the plasma membrane and the subsequent phosphorylation of Akt/PKB and AS160. This leads to the translocation of glucose transporter proteins (GLUT4) from intracellular vesicles to the plasma membrane and increased glucose uptake (reviewed in Ref. [29]). Negative control and down regulation of this pathway is conducted mainly by PTP, which dephosphorylate their target proteins in the pathway. H_2O_2 can either inhibit or activate the pathway dependent on the concentration [30–32]. H_2O_2 treatment of cells results in the oxidation of numerous PTP, such as PTPB1, SHP2 and PTEN, which negatively regulate the insulin signalling pathway [33–35]. Redox sensitive cysteine residues in PTPs have been identified [33,35] but again, it is unknown if intracellular H_2O_2 oxidises these directly or through redox-sensitive intermediaries.

3. ***Peroxisome proliferator-activated receptor gamma (PPAR-γ).***

PPAR-γ is a major regulator of lipid metabolism and mitochondrial genes and is a transcription factor for a large number of genes controlling mechanisms such as lipid storage/lipogenesis, energy expenditure and the OXPHOS pathway. Protein levels of PPAR-γ are increased in skeletal muscle by chronic exercise, as are those of its transcriptional co-activator PGC1-α [36,37]. Both PPAR-γ and PGC1-α are known to be modulated by treatment of cells with H_2O_2, but whether this occurs through direct oxidation or via redox-sensitive intermediaries is unknown [38–40].

4. ***Nuclear factor-κB (NF-κB).***

NF-κB is a key regulator of inflammatory responses and is activated by contractile activity in skeletal muscle, typically via the pathway known as the canonical NF-κB signalling pathway, which is mediated by IKK and IκB. The immediate signalling events following muscle contraction are poorly understood but result in the phosphorylation and activation of the IκB-kinase (IKK) complex, which then phosphorylates IκB. In unstimulated cells IκB exists in a complex with the NF-κB subunits, p65 and p50, sequestering them in cytosol. Phosphorylation of IκB targets it for ubiquitination, ultimately leading to its degradation by the proteosome. NF-κB is subsequently released and able to translocate to the nucleus where it acts as a transcription factor for genes involved in a wide variety of responses associated with inflammation and stress, as well as antioxidant proteins such as catalase, TRX, MnSOD and GPX (reviewed in Ref. [41]). The impact of oxidation on the NF-κB signalling has been widely studied and several proteins in the canonical NF-κB pathway are known to be regulated by H_2O_2 (reviewed in Ref. [42]). As with the other signalling pathways discussed, it is not known whether H_2O_2 directly oxidises these target proteins, or acts through intermediary redox-sensitive proteins.

This apparent congruence between the *ex-vivo* effects of H_2O_2 on signalling pathways and activation of these same signalling pathways by contractile activity *in vivo* has been cited as evidence for redox regulation playing a role in activation of these pathways during exercise *in vivo*, but comparisons of *in vivo* concentrations of H_2O_2 with those used to activate key signalling molecules in cell culture do not support this thesis. Thus, H_2O_2 has been shown to activate NF-κB [43,44], p38-MAPK [25] and many other signalling molecules [45], but the key signalling molecules examined are relatively unreactive with H_2O_2 and studies have utilised H_2O_2 concentrations typically in the range 10^{-4}-10^{-3}M (i.e. 100 μM – 1 mM) which are unlikely to have any *in vivo* relevance.

5. Concentrations of H_2O_2 in skeletal muscle fibres

Sies has concluded that the intracellular H_2O_2 concentration in most cells is in the order of 10^{-9}-10^{-8}M (1–10nM) [46], but few authors have attempted to evaluate likely concentrations in skeletal muscle fibres at rest or during contractions. Palomero and colleagues [5] compared the relative increase in CM-DCF oxidation observed following 15 min contractile activity in isolated intact FDB fibres of mice with that seen in the same fibres following exposure to 10^{-6}M (i.e. 1 μM) H_2O_2. The protocol of contractions used [5] had previously been shown to induce release of superoxide and nitric oxide from muscle cells in culture and mice *in vivo* [47,48], to lead to a fall in muscle glutathione and protein thiol content [49], and to lead to the induction of redox-regulated adaptive responses [50] when applied to intact muscles *in*

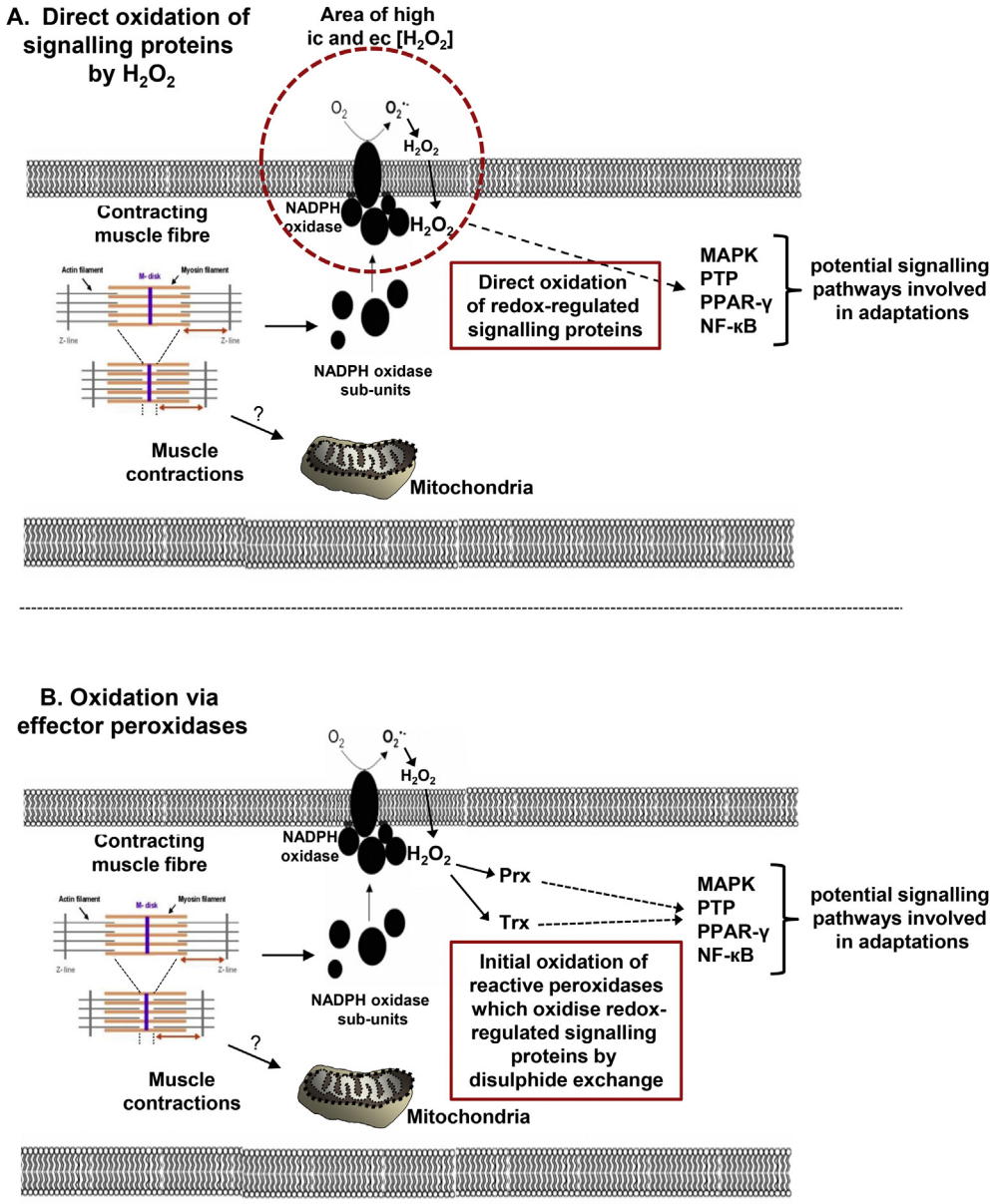

Fig. 1. Schematic representation of the 2 potential routes by which H_2O_2 generated in contracting muscle fibres may activate key cell signalling pathways. **(A)** Generation of H_2O_2 by NADPH oxidase 2 on the plasma or T-tubule membrane occurs initially on the outside of the membrane but generates a substantial local increase in H_2O_2 concentration on both sides of the membrane that is sufficient to directly oxidise, so-called, "redox-sensitive" signalling proteins in key pathways. **(B)** Local generation of H_2O_2 is insufficient to directly oxidise the "redox-sensitive" signalling proteins in key pathways, but can react with highly sensitive peroxidases (e.g. Prx or Trx) which then further oxidise less sensitive proteins by disulphide exchange leading to indirect activation of the signalling pathways.

vivo. Surprisingly the degree of increase in intracellular CM-DCF fluorescence induced by the contraction protocol was less than that seen following exposure of the fibers to 10^{-6}M (1 μM) H_2O_2. Antunes and Cadenas [51] had previously calculated that, in Jurkat cells, an extracellular:cytosolic gradient of ~7:1 would be rapidly established following addition of external H_2O_2 and Palomero et al., [5] applied this factor to muscle fibres to calculate likely intracellular H_2O_2 concentrations in muscle fibres. Thus, if these data are also applicable to skeletal muscle fibers, the likely change in intracellular H_2O_2 following exposure to 10^{-6}M H_2O_2 to the extracellular medium is ~10^{-7}M (100 nM) H_2O_2 and the rise in CM-DCFH oxidation seen following contractile activity was lower than that induced by addition of 10^{-6}M (1 μM) H_2O_2 to the medium. Thus, it can be inferred that the absolute level of cytosolic H_2O_2 in muscle fibers that was achieved following contractile activity was small and equivalent to less than 10^{-7}M (100 nM). The implication of these data is that the increase in H_2O_2 seen with contractions is so low that the activation, or redox regulation, of adaptive cell signalling pathways by H_2O_2 cannot occur through non-specific direct oxidation of redox-sensitive, but relatively unreactive signalling proteins and must involve more specific pathways.

6. Potential mechanisms by which H_2O_2 might act to stimulate signalling pathways at the low intracellular concentrations found in contracting muscle fibres *in vivo*

There are two main theories concerning how physiological levels of H_2O_2 might oxidise thiols in redox-sensitive proteins [52]. The first postulates direct oxidation and some authors have argued that this is facilitated by proximity of the target protein to the source of generation of H_2O_2 where local concentrations may be increased [53], but computational modelling has indicated that even near sites of H_2O_2 generation the concentrations are far too low to oxidise typical redox targets [54]. A derivation of this hypothesis is that local scavengers of H_2O_2 become rapidly oxidised and inactivated subsequently permitting a local increase in local H_2O_2 concentration to micromolar levels (the "floodgate" hypothesis). The major local scavengers of H_2O_2 which can react with H_2O_2 at the concentrations found intracellularly are glutathione peroxidase, peroxiredoxins [55] and thioredoxins (Trx). Peroxiredoxins (Prx) are potentially attractive candidates to play this role since there is substantial evidence that Prxs can become hyperoxidised leading to a loss of peroxidase activity which is in accord with this

hypothesis [55]. Prx are a family of antioxidant enzymes which reduce hydroperoxides to water in the presence of electron donors and are generally considered to be important antioxidant enzymes in the cytosol (Prx1, Prx2, Prx5), mitochondria (Prx3, Prx5) and endoplasmic reticulum (Prx4).

The second possibility involves the utilisation of highly oxidisable effectors to transfer oxidative equivalents directly from a H_2O_2-sensitive thiol peroxidase to a specific target protein through direct protein-protein contact allowing conversion of the oxidising equivalent from H_2O_2 into a disulphide bond that can be subsequently transmitted to other substrates through formation of intermolecular disulphides. It has been shown that thiol peroxidases can transmit oxidising equivalents to a specific target protein to facilitate H_2O_2 signalling [13]. This mechanism has been documented in yeast [56,57], but only recently been shown to occur in activation of a transcription factor by H_2O_2 in animal cells [13]. Key components of such signalling pathways are Prx and thioredoxins (Trx [58]). Importantly and in contrast to the relative poor reactivity of the proteins involved in activating transcription factors discussed previously (e.g. MAPK, PTP, PPAR-γ and NF-κB), Prx are several order of magnitude more reactive with H_2O_2 [13] and thus can potentially react with, and reduce H_2O_2 at the low H_2O_2 concentrations found in muscle fibres. Studies in non-muscle cells indicate that Prxs can function as a signal peroxidase to activate specific pathways. Prx1 has been shown to activate the transcription factor ASK1 [26] and Prx2 forms a redox relay with the transcription factor STAT3 such that oxidative equivalents flow from Prx2 to STAT3 generating disulphide-linked STAT3 oligomers with modified transcriptional activity [13]. These 2 possible mechanisms by which H_2O_2 may oxidise and activate key signalling pathways in muscle are shown schematically in Fig. 1.

In summary, although the possibility that Prx or Trx can play "effector" roles in redox signalling in skeletal muscle in response to exercise does not appear to have been explored, current knowledge of H_2O_2 concentrations suggest that the basic concept of direct oxidation of "redox-regulated" signalling proteins in multiple pathways by H_2O_2 is untenable. Identification of potential effectors of H_2O_2 signalling in skeletal muscle may provide a series of novel targets by which redox signalling can be modified to allow optimisation of the beneficial effects of exercise to help maintain muscle mass and function in the elderly and other groups at risk from the effects of muscle weakness and loss.

Declaration of competing interest

None of the authors have any relevant conflict of interest pertaining to this publication. The research work described has been funded by a number of external public bodies over several years following rigorous independent peer-review.

Acknowledgements

The authors would like to thank multiple current and former collaborators for their input into the ideas described here and to acknowledge generous on-going financial support from the Medical Research Council, Versus Arthritis and the US National Institute on Aging (NIH).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2020.101484.

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