ROS

RESEARCH HIGHLIGHTS

Photobiomodulation: Newly Discovered Actions in Resistance Exercise

Simone M. Sunemi[1], Flávio André Silva[2,3], Ednei Luiz Antonio[2], Paulo José Ferreira Tucci[2], and Andrey Jorge Serra[1,2]

[1]Universidade Nove de Julho, Programa de Pós-graduação em Biofotônica Aplicada as Ciências da Saúde, São Paulo–SP, Brazil; [2]Universidade Federal de São Paulo, Programa de Pós-graduação em Cardiologia, São Paulo–SP, Brazil; [3]Universidade Adventista de São Paulo, São Paulo–SP, Brazil

Correspondence: andreyserra@gmail.com (A.J.S.)

Sunemi SM et al. Reactive Oxygen Species 7(21):148–153, 2019; ©2019 Cell Med Press
http://dx.doi.org/10.20455/ros.2019.829
(Received: December 19, 2018; Revised: January 14, 2019; Accepted: January 24, 2019)

ABSTRACT | Many of the studies, that have evaluated the role of photobiomodulation (PBM) in alleviating excessive oxidative stress induced by exercise, were carried out in the setting of aerobic activities. In line with this notion, the aim of this Research Highlights article was to summarize the new role of PBM in the oxidative stress resulting from anaerobic exercise. Thus, this Research Highlights article briefly summarizes the findings reported in a recent article published in *Oxidative Medicine and Cellular Longevity* (February 18, 2018; doi: 10.1155/2018/5763256) by de Oliveira et al., which reported that low-level laser therapy (LLLT) can protect skeletal muscles from oxidative stress induced by acute resistance exercise (RE). In fact, rats that underwent laser irradiation in the gastrocnemius muscle prior to RE bout showed a similar lipoperoxidation level to that of non-exercised rats. Animals in the LLLT group were also protected from attack by reactive oxygen species on their amino acids, as was revealed by the changes in the oxidized protein content. This study by de Oliveira et al. provides novel insights into the PBM process, which acts as a suppressor of the excessive oxidative stress evoked by RE.

KEYWORDS | Low-level laser therapy; Muscular damage; Photobiomodulation; Reactive oxygen species; Resistance exercise

ABBREVIATIONS | CAT, catalase; GPx, glutathione peroxidase; LED, light emitting diode; LLLT, low-level laser therapy; NADPH, nicotinamide adenine dinucleotide phosphate; PBM, photobiomodulation; RE, resistance training; ROS, reactive oxygen species; SOD, superoxide dismutase

CONTENTS

1. OVERVIEW

It is well-known that exercise training has multiple health benefits. However, acute exercise and subsequent recovery are marked by the disruption of homeostasis. For example, muscle damage and inflammation are increased after an exercise bout [1], with a possible increase in reactive oxygen species (ROS) in a manner dependent on the type, duration, and load of the exercise [2].

In aerobic exercise, the increase in O_2 consumption is an important factor that leads to the generation of oxidizing agents [3]. Thus, a more pronounced pro-oxidative status has been reported for high-intensity aerobic activities [4]. Likewise, it has been established that acute anaerobic exercise induces oxidative stress changes [5], a state that occurs even in the presence of elevated levels of antioxidant molecules [6]. Multiple factors have been considered to trigger ROS production, such as activation of the electron transport chain, increase of xanthine oxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and tissue ischemia/reperfusion derived from muscle contraction/relaxation [7].

Notwithstanding, ROS at low levels, a phenomenon similar to hormesis, play an important role in exercise-induced physiological adaptation [8]. Conversely, excessive oxidative stress can result in impaired physical performance and maladaptive muscle recovery [2].

Photobiomodulation (PBM) is a low power, non-thermal delivery of photons in the visible or near infrared spectrum that stimulates, heals, regenerates, or protects tissues [9, 10]. PBM has multiple applications in medicine including light emitting diodes (LED) and low-level laser therapy (LLLT) to treat articular, cardiovascular, dermatological, ocular, metabolic, muscular, neurological, and rheumatologic diseases.

Recently, PBM appeared as a new alternative to modulate the excessive oxidative stress induced by exercise. Several benefits were reported, including: (1) lowering concentrations of proinflammatory cytokines and decreasing lipoperoxidation and muscle damage; (2) increasing antioxidant enzyme activities; and (3) delaying muscle fatigue [11]. It is worth mentioning that most studies have evaluated the role of PBM in modulating oxidative stress in light of aerobic exercise. In this regard, we found lower carbonyl protein levels in dystrophic mice when LLLT was applied prior to high-intensity exercise on a treadmill [12]. With a similar exercise approach, we recently showed that LLLT inhibited the increase of thiobarbituric acid-reactive substances and restored the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the gastrocnemius muscle of diabetic rats [13]. Likewise, it would also be important to determine the role of PBM in the regulation of muscle oxidative stress during anaerobic exercise. To our knowledge, the study of Ferraresi et al. [11], for the first time, attributed a potential physiological function to PBM that appears to increase the muscle antioxidant status in mice submitted to a resistance training (RE) associated with LED. This finding led to the hypothesis that an analogous effect could be noticed when PBM is applied prior to acute RE.

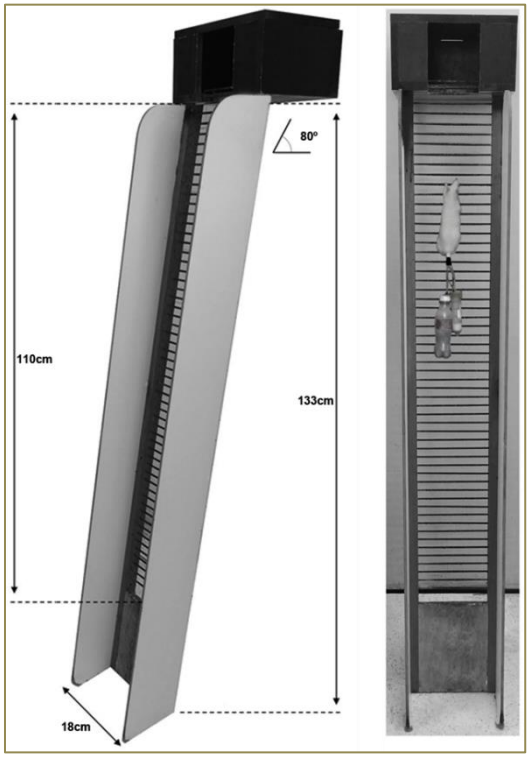

FIGURE 1. Resistance weighted ladder climb.

Based on the above hypothesis, this Research Highlights article discusses and summarizes the recent manuscript of de Oliveira et al. [14], concerning the influence of LLLT on oxidative stress in rats subjected to a high-intensity RE bout.

2. AN IMPORTANT STUDY

In an article published in 2018 in the journal, *Oxidative Medicine and Cellular Longevity*, de Oliveira et al. [14] reported a new role for LLLT in protecting the skeletal muscles from oxidative stress induced by RE, in which the PBM spectrum found in the study of Ferraresi et al. is expanded [11]. In their study, de Oliveira et al. [14] applied a RE bout on rats climbing a vertical ladder of 54 steps carrying 100% of the maximum load (**Figure 1**); one of the animal groups was previously irradiated with LLLT at the gastrocnemius muscle. The authors showed that the LLLT group had similar lipoperoxidation levels to those of the non-exercised rats (**Figure 2A**). Additionally, LLLT rats were protected from ROS attack on their amino acids, as revealed by the overall protein oxidation content in the muscles. The authors did not investigate the impact of this finding, but it is well known that high oxidation may result in post-translational changes in the proteins that affect muscle function [15].

In view of the antioxidative mechanism, de Oliveira et al. [14] examined the key enzymes affecting muscle activity, such as SOD, catalase (CAT), and GPx. SOD catalyzes the dismutation of superoxide to produce hydrogen peroxide (H_2O_2) and molecular O_2, and CAT catalyzes the degradation of H_2O_2 to H_2O and O_2 [15–17]. Ultimately, GPx reduces H_2O_2 or an organic peroxide to H_2O or an alcohol [8]. Despite the fact that the study by de Oliveira et al. [14] did not show any alteration in CAT activity due to RE or LLLT, it showed clear changes in the activities of the other enzymes (**Figure 2B**). Indeed, SOD and GPx activities were upregulated in exercised animals treated with LLLT compared to those submit-

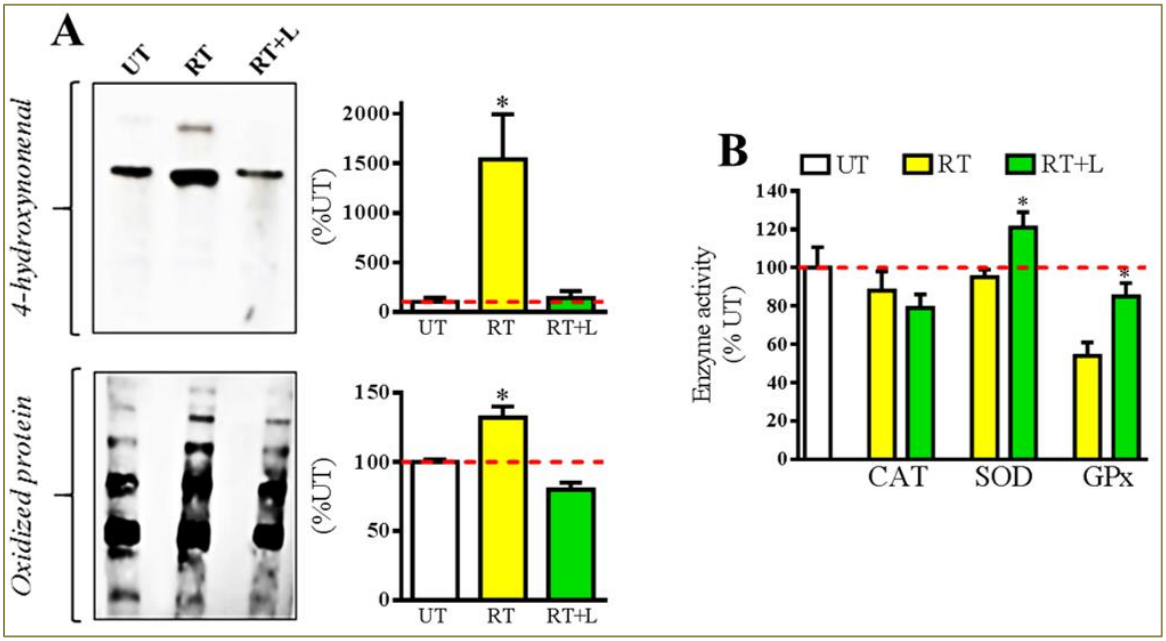

FIGURE 2. Role of low-level laser therapy (LLLT) in the biosynthesis of oxidative stress markers in untrained rats (UT), rats that underwent a resistance exercise session (RT), and rats that were subject to LLLT prior to exercise (RT+L). As illustrated, exercise increases 4-hydroxynonenal and oxidation protein levels in skeletal muscle (Panel A). In contrast, the increase in lipoperoxidation and oxidation of proteins can be prevented when LLLT is applied before exercise. It is noteworthy that the antioxidant effects of LLLT are linked to increased activity of the enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) but have no effect on catalase (CAT) (Panel B). The illustrations have been modified from the original manuscript by de Oliveira et al. [14]. $*$, $p < 0.05$ compared to the UT and RT+L groups.

ted only to RE. These findings indicate that LLLT preconditioning increases muscle protection against excessive oxidative stress induced by a high-intensity RE session, delays the impairments of muscle contractility that leads to fatigue [18], and hence contributes to improved training response. Moreover, lower oxidative stress could be linked to LLLT ability to attenuate muscle damage induced by RE as previously reported by the same research group [1].

3. CONCLUSION AND PERSPECTIVES

There are data suggesting that PBM, especially LLLT, may alleviate the oxidative effects of acute exercise. In line with this notion, there is more information on LLLT attenuating oxidative stress triggered by aerobic rather than by anaerobic exercise. In response to this issue, the study discussed in this ROS Research Highlights [14] adds novelty to the concept that application of LLLT prior to a high-intensity RE bout may attenuate oxidative stress in rats. Oxidative stress mitigation was based on the finding of reduced 4-hydroxynonenal content (**Figure 3**), one of the well-studied end products of lipoperoxidation [19]. Moreover, protein carbonylation was not increased in exercised rats that were previously irradiated with LLLT. Therefore, this innovative study not only extends the use of LLLT beyond aerobic exercise but also provides insights for future clinical studies applying PBM to counteract the supraphysiological production of ROS during RE.

Notwithstanding, among the LLLT parameters that could be used in clinical practice, the biphasic dose-

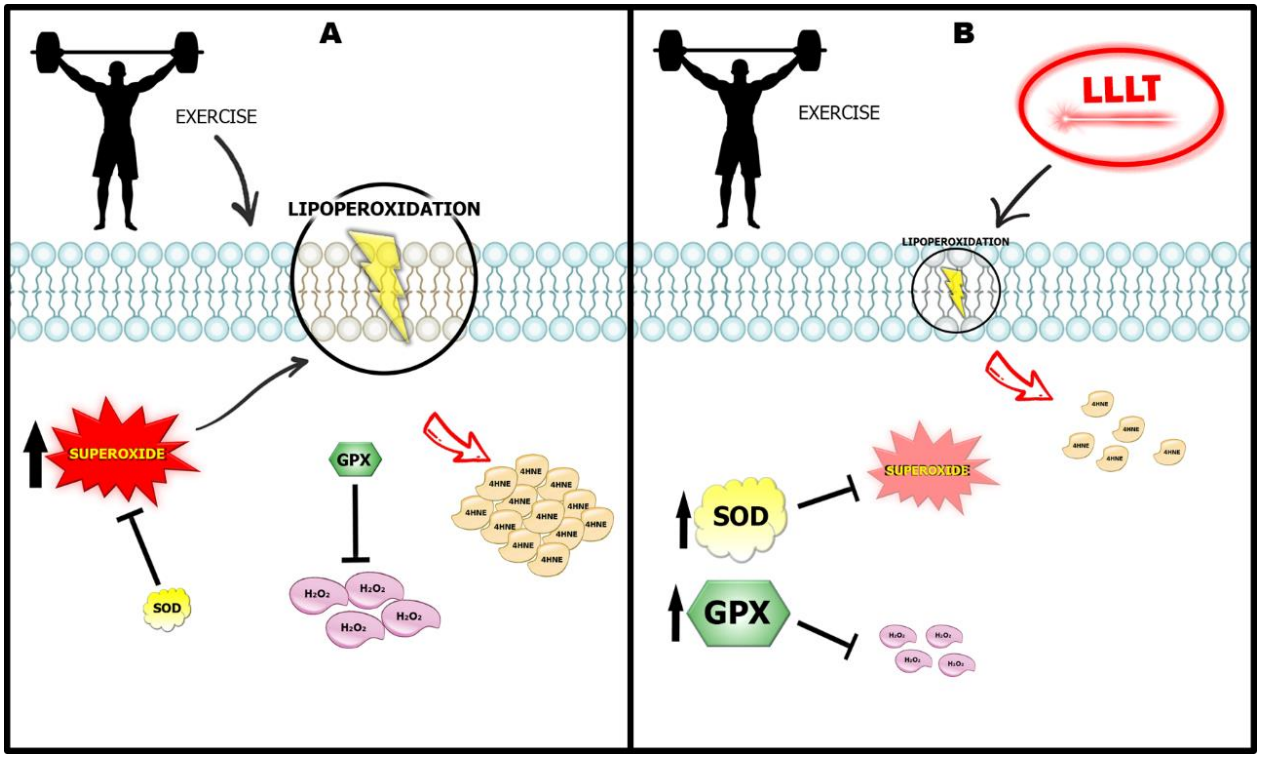

FIGURE 3. Oxidative stress in response to a high-intensity resistive exercise (RE) bout and repercussion of the low-intensity laser (LLLT). (A) The RE triggers the increase of oxidative substances such as superoxide and H_2O_2. This causes lipoperoxidation of the cellular membrane, which releases 4-hydroxynonenal (4-HNE). (B) Conversely, when LLLT is applied prior to exercise, it increases the enzymatic activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx). This enzymatic mechanism can alleviate the oxidative stress induced by RE.

response is a feature that should be evaluated in the future. This issue is based on the principle that a very low dose of light has no biological effect, but a slightly greater dose has a positive effect that continues until it reaches a plateau [20]. Thus, the best LLLT parameter that modulates oxidative stress induced by RE has to be determined. Another issue is whether pre- or post-RE LLLT application has a similar effect on oxidative stress. The reason for this inquiry originates from a study published by dos Reis et al. [21]. The authors subjected 27 healthy men to exercise fatigue involving all major lower limb muscles. Post-exercise LLLT application significantly decreased the serum lactate and creatine kinase levels compared to exercised non-irradiated men. On the other hand, pre-fatigue laser had no significant effect on lactate and creatine kinase levels. Ultimately, the main issue is that an increase in oxidative stress plays a key role in several cellular signaling pathways involved in muscle adaptation [22]. This is consistent with hormesis, wherein exercise modulates ROS to induce favorable physiological adaptations [7]. Consequently, how LLLT-induced oxidative stress prevention influences muscle adaptation to RE remains unclear and needs to be studied further.

ACKNOWLEDGMENTS

The authors would like to thank São Paulo Research Foundation–FAPESP (#2018/06865-87) and National Council for Scientific and Technological Development–CNPq (#305527/2017-7). All of the authors declare no conflicts of interest.

REFERENCES

1. de Oliveira HA, Antonio EL, Silva FA, de Carvalho PTC, Feliciano R, Yoshizaki A, et al. Protective effects of photobiomodulation against resistance exercise-induced muscle damage and inflammation in rats. *J Sports Sci* 2018; 36(20):2349–57. doi: 10.1080/02640414.2018.1457419.
2. Steinbacher P, Eckl P. Impact of oxidative stress on exercising skeletal muscle. *Biomolecules* 2015; 5(2):356–77. doi: 10.3390/biom5020356.
3. Schneider CD, Oliveira AR. Oxygen free radicals and exercise: mechanisms of synthesis and adaptation to the physical training. *Rev Bras Med Esporte* 2004; 10(4):308–13. doi: 10.1590/S1517-86922004000400008.
4. Mastaloudis A, Morrow JD, Hopkins DW, Devaraj S, Traber MG. Antioxidant supplementation prevents exercise-induced lipid peroxidation, but not inflammation, in ultramarathon runners. *Free Radic Biol Med* 2004; 36(10):1329–41. doi: 10.1016/j.freeradbiomed.2004.02.069.
5. Wiecek M, Szymura J, Maciejczyk M, Kantorowicz M, Szygula Z. Anaerobic exercise-induced activation of antioxidant enzymes in the blood of women and men. *Front Physiol* 2018; 9:1006. doi: 10.3389/fphys.2018.01006.
6. Deminice R, Sicchieri T, Payao PO, Jordao AA. Blood and salivary oxidative stress biomarkers following an acute session of resistance exercise in humans. *Int J Sports Med* 2010; 31(9):599–603. doi: 10.1055/s-0030-1255107.
7. Radak Z, Zhao Z, Koltai E, Ohno H, Atalay M. Oxygen consumption and usage during physical exercise: the balance between oxidative stress and ROS-dependent adaptive signaling. *Antioxid Redox Signal* 2013; 18(10):1208–46. doi: 10.1089/ars.2011.4498.
8. Kozakowska M, Pietraszek-Gremplewicz K, Jozkowicz A, Dulak J. The role of oxidative stress in skeletal muscle injury and regeneration: focus on antioxidant enzymes. *J Muscle Res Cell Motil* 2015; 36(6):377–93. doi: 10.1007/s10974-015-9438-9.
9. Hamblin MR. Shining light on the head: Photobiomodulation for brain disorders. *BBA Clin* 2016; 6:113–24. doi: 10.1016/j.bbacli.2016.09.002.
10. Liebert A, Krause A, Goonetilleke N, Bicknell B, Kiat H. A Role for photobiomodulation in the prevention of myocardial ischemic reperfusion injury: a systematic review and potential molecular mechanisms. *Sci Rep* 2017; 7:42386. doi: 10.1038/srep42386.
11. Ferraresi C, Parizotto NA, Pires de Sousa MV, Kaippert B, Huang YY, Koiso T, et al. Light-emitting diode therapy in exercise-trained mice increases muscle performance, cytochrome c oxidase activity, ATP and cell proliferation. *J Biophotonics* 2015; 8(9):740–54. doi: 10.1002/jbio.201400087.
12. Silva AA, Leal-Junior EC, D'Avila Kde A, Serra

AJ, Albertini R, Franca CM, et al. Pre-exercise low-level laser therapy improves performance and levels of oxidative stress markers in mdx mice subjected to muscle fatigue by high-intensity exercise. *Lasers Med Sci* 2015; 30(6):1719–27. doi: 10.1007/s10103-015-1777-7.
13. Frigero M, Dos Santos SA, Serra AJ, Dos Santos Monteiro Machado C, Portes LA, Tucci PJF, et al. Effect of photobiomodulation therapy on oxidative stress markers of gastrocnemius muscle of diabetic rats subjected to high-intensity exercise. *Lasers Med Sci* 2018; 33(8):1781–90. doi: 10.1007/s10103-018-2540-7.
14. de Oliveira HA, Antonio EL, Arsa G, Santana ET, Silva FA, Junior DA, et al. Photobiomodulation leads to reduced oxidative stress in rats submitted to high-intensity resistive exercise. *Oxid Med Cell Longev* 2018; 2018:5763256. doi: 10.1155/2018/5763256.
15. Gilliam LA, Lark DS, Reese LR, Torres MJ, Ryan TE, Lin CT, et al. Targeted overexpression of mitochondrial catalase protects against cancer chemotherapy-induced skeletal muscle dysfunction. *Am J Physiol Endocrinol Metab* 2016; 311(2):E293–301. doi: 10.1152/ajpendo.00540.2015.
16. Bird HZ, Hopkins RZ. Nanomaterials for selective superoxide dismutation. *React Oxyg Species (Apex)* 2015; 1(1):59–64. doi: 10.20455/ros.2016.811.
17. Chelikani P, Fita I, Loewen PC. Diversity of structures and properties among catalases. *Cell Mol Life Sci* 2004; 61(2):192–208. doi: 10.1007/s00018-003-3206-5.
18. He F, Li J, Liu Z, Chuang CC, Yang W, Zuo L. Redox Mechanism of reactive oxygen species in exercise. *Front Physiol* 2016; 7:486. doi: 10.3389/fphys.2016.00486.
19. Zhong H, Yin H. Role of lipid peroxidation derived 4-hydroxynonenal (4-HNE) in cancer: focusing on mitochondria. *Redox Biol* 2015; 4:193–9. doi: 10.1016/j.redox.2014.12.011.
20. Hamblin MR. Mechanisms and mitochondrial redox signaling in photobiomodulation. *Photochem Photobiol* 2018; 94(2):199–212. doi: 10.1111/php.12864.
21. Dos Reis FA, da Silva BA, Laraia EM, de Melo RM, Silva PH, Leal-Junior EC, et al. Effects of pre- or post-exercise low-level laser therapy (830 nm) on skeletal muscle fatigue and biochemical markers of recovery in humans: double-blind placebo-controlled trial. *Photomed Laser Surg* 2014; 32(2):106–12. doi: 10.1089/pho.2013.3617.
22. Kerksick CM, Zuhl M. Mechanisms of oxidative damage and their impact on contracting muscle. In: *Antioxidants in Sport Nutrition* (M Lamprecht). CRC Press/Taylor & Francis, Boca Raton, FL, USA. 2015, pp. 1-16.