18 Timmons, J. A., Gustafsson, T., Sundberg, C. J., Hultman, E., Kaijser, L., Chwalbinska-Moneta, J., Constantin-Teodosiu, D., Macdonald, I. A. and Greenhaff, P. L. (1998) J. Clin. Invest. **101**, 79–85
19 Harris, R. C., Foster, C. V. L. and Hultman, E. (1987) J. Appl. Physiol. **63**, 440–442
20 Howlett, R. A., Heigenhauser, G. J. F., Hultman, E., Hollidge-Horvat, M. G. and Spriet, L. (1999) Am. J. Physiol. **277**, E18–E25
21 Roberts, P. A., Loxham, S. J. G., Poucher, S. M., Constantin-Teodosiu, D. and Greenhaff, P. L. (2000) J. Physiol. (Cambridge, U.K.) **523P**, 12P
22 Martin, B. J., Robinson, S., Wiegman, D. L. and Aulick, L. H. (1975) Med. Sci. Sport **7**, 146–149
23 Essen, B. and Kaijser, L. (1978) J. Physiol. (Cambridge, U.K.) **281**, 499–511
24 Genovely, H. and Stamford, B. A. (1982) Eur. J. Appl. Physiol. Occup. Physiol. **48**, 1394–1403
25 Robergs, R. A., Pascoe, D. D., Costill, D. L., Fink, W. J., Chwalbinska-Montera, J., Davis, J. A. and Hickner, R. (1991) Med. Exercise Sport Sci. **23**, 37–43
26 Campbell-O'Sullivan, S. P., Constantin-Teodosiu, D., Peirce, N. and Greenhaff, P. L. (2002) J. Physiol. (Cambridge, U.K.), **538**, 931–939

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Exercise, free radicals and oxidative stress

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Abstract

This article reviews the role of free radicals in causing oxidative stress during exercise. High intensity exercise induces oxidative stress and although there is no evidence that this affects sporting performance in the short term, it may have longer term health consequences. The mechanisms of exercise-induced oxidative stress are not well understood. Mitochondria are sometimes considered to be the main source of free radicals, but *in vitro* studies suggest they may play a more minor role than was first thought. There is a growing acceptance of the importance of haem proteins in inducing oxidative stress. The release of metmyoglobin from damaged muscle is known to cause renal failure in exercise rhabdomyolysis. Furthermore, levels of methaemoglobin increase during high intensity exercise, while levels of antioxidants, such as reduced glutathione, decrease. We suggest that the free-radical-mediated damage caused by the interaction of metmyoglobin and methaemoglobin with peroxides may be an important source of oxidative stress during exercise.

Key words: haemoglobin, mitochondrion, myoglobin, oxygen, superoxide.

Abbreviations used: ROS, reactive oxygen species; $UQH^{\bullet -}$, ubisemiquinone radical; XOD, xanthine oxidase.

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Introduction: free radicals and oxidative stress

Free radicals, chemical species containing one or more unpaired electrons that are capable of independent existence, are produced in all living cells. Most radicals that occur *in vivo* either are, or originate from, reactive oxygen species (ROS) or reactive nitrogen species. ROS include oxygen-based free radicals, e.g. superoxide ($O_2^{\bullet -}$), hydroxyl ($OH^{\bullet}$), alkoxyl ($RO^{\bullet}$), peroxyl ($ROO^{\bullet}$) and hydroperoxyl ($ROOH^{\bullet}$). Other ROS (e.g. hydrogen peroxide and lipid peroxides) can be converted into free radicals by transition metals, either free in the cell or protein-bound. Reactive nitrogen species include the free radicals nitric oxide ($NO^{\bullet}$) and nitrogen dioxide ($NO_2^{\bullet}$) and the potent oxidant peroxynitrite ($ONOO^-$).

Free radicals have the potential to react with a variety of chemical species, making them ideal for a wide range of biological functions in cell signalling (e.g. $NO^{\bullet}$ [1]) and enzymology (e.g. witness the role of protein-bound free radicals in the mechanism of a range of reductases, peroxidases, catalases and oxidases [2]). However, ROS are also inadvertently produced in the body, by a variety of mechanisms [3]. The majority of free radicals produced *in vivo* are oxidants, which are capable of oxidizing a range of biological molecules, including carbohydrates, amino acids, fatty acids and nucleotides. As it is impossible to prevent all free radical production *in vivo*, it is not surprising that

a range of antioxidant defences have evolved in the body. Both enzymic and non-enzymic antioxidants are present. Antioxidant enzymes include superoxide dismutase, glutathione peroxidase and catalase. The main non-enzymic antioxidants include GSH, vitamin C and vitamin E. The antioxidant defences of the body are usually adequate to prevent substantial tissue damage. However, there is not an excess of antioxidant defences, and an overproduction of free radicals or a drop in the level of the antioxidant defences will lead to an imbalance and cause deleterious effects, a situation known as oxidative stress. There are clear indications that exercise has the potential to increase free radical production and lead to oxidative stress. This review summarizes the evidence in favour of exercise inducing oxidative stress and the possible mechanisms involved [4]. In particular the role of haem iron (in haemoglobin and myoglobin) as a novel inducer and transducer of oxidative stress will be considered.

Possible mechanisms of free radical production during exercise

There is an increase in the release of catecholamine hormones during exercise, the auto-oxidation of which can produce free radicals. Muscle damage subsequent to exercise (e.g. in delayed onset muscle soreness) can cause inflammation and release of superoxide from the neutrophil NADPH oxidase. However, it is usually stated that one of the most important source of ROS during exercise is mitochondrial superoxide production, via side-reactions of flavin or ubisemiquinone ($UQH^{\bullet -}$) radicals with oxygen [5,6]

$$UQH^{\bullet -} + O_2 = UQ + O_2^{\bullet -} + H^+ \qquad (1)$$

Physical exercise increases energy demand to a large extent, and to provide for this oxygen uptake by the body may increase by as much as 15-fold, and oxygen flux through active muscle may increase by approx. 100-fold above the resting values. Consequently, it is argued that a substantial increase in the production of mitochondrial $O_2^{\bullet -}$ is inevitable. This argument is flawed on two counts. First, the rate of $O_2^{\bullet -}$ production via eqn (1) is linearly dependent on the oxygen tension and this leads to decreased $O_2^{\bullet -}$ production [7] as the pO_2 is decreased (as would be expected in working muscle). Secondly, the steady state of the other substrate in eqn (1), $UQH^{\bullet -}$, does not increase automatically as the flux through the mitochondrial electron transfer chain increases. In fact decreasing the mitochondrial membrane potential (as occurs when muscle mitochondria increase their rate of ATP production) decreases mitochondrial free radical production [7,8]. This occurs despite a dramatic increase in oxygen consumption rates. It should be noted that the majority of studies showing high rates of mitochondrial superoxide production *in vitro* are in inhibited mitochondria at supraphysiological pO_2, i.e. exactly the opposite conditions to those found in exercising muscle. These *in vitro* studies do not disprove that mitochondria may be a source of free radicals during exercise. However, *in vivo* studies need to address this question directly, rather than assuming that more mitochondrial oxygen consumption means more mitochondrial free-radical production.

An alternative mechanism by which exercise may promote free radical production involves ischaemia-reperfusion. Intense exercise is associated with transient tissue hypoxia in several organs (e.g. kidneys and splanchnic region), as blood is shunted away to cover the increased blood supply in active skeletal muscles and the skin. Beside this, during exercise performed at intensities above $\dot{V}O_2max$, muscle fibres may undergo relative hypoxia, as oxygen supply cannot match the energy requirements [9]. Re-oxygenation of these tissues occurs after the cessation of exercise, and this can be associated with the production of ROS [4,9]. One way in which reperfusion could lead to an increased ROS production is through the conversion of xanthine dehydrogenase to xanthine oxidase (XOD). Both xanthine dehydrogenase and XOD catalyse the degradation of hypoxanthine into xanthine, and subsequently into urate. However, only XOD produces $O_2^{\bullet -}$ in the final step of this reaction. Production of ROS via this mechanism leads to oxidative stress several hours after exercise, and is not restricted to skeletal muscle [9]. Interestingly, it was shown in a recent study that free radical markers of oxidative stress were reduced significantly in animals and humans after the addition of the XOD inhibitor, allopurinol [10]. XOD may be more important than mitochondria as a source of exercise-induced free radicals.

Does exercise induce oxidative stress?

In 1978, Dillard et al. [11] were the first to demonstrate that physical exercise can lead to an increase in lipid peroxidation. They observed a 1.8-fold increase in exhaled pentane levels, a possible by-product of oxidative lipid damage, after 60 min of cycling at 25–75 % of $\dot{V}O_2max$.

Since then, an increasing body of evidence has accumulated to support the hypothesis that physical exercise has the potential to increase free radical production and lead to oxidative stress. Measuring free radical production directly is difficult, primarily because of the short life-span of these species. The use of free radical spin traps can increase this life-span and there have been recent studies demonstrating that blood removed from an exercising individual has an enhanced ability to trap free radicals when assayed *ex vivo* [12,13]. The majority of studies investigating the effects of exercise on oxidative stress have, however, focused on markers of free radical induced tissue damage. Indications of increased damage to lipids [11–16], protein [17] and DNA [15,18,19] with exercise have been well documented. Exercise-induced changes in levels of antioxidants have also been studied, but their significance to oxidative stress is harder to determine. While oxidative stress could cause a primary decrease in antioxidants, mobilization from secondary sources elsewhere in the body might result in an apparent increase. Thus, it has been shown fairly consistently that the GSH:GSSG ratio in the blood decreases with exercise [20,21], whereas plasma levels of vitamins C and E tend to increase [21–24]. Therefore, although changes in oxidation state or concentration of antioxidants can point to impaired antioxidant defences, they do not necessarily indicate tissue damage [4]. It is unclear what causes these changes, or to what extent they influence oxidative stress. A rise in plasma antioxidant levels might enhance the antioxidant defences in the blood, but could possibly impair defences at the sites from which they are mobilized.

Some investigators have failed to observe any signs of exercise-induced oxidative stress [25–27]. This could be due to a number of reasons. First, the use of different test-subjects might influence the findings of different studies; factors such as training status, age and gender could all play a role. Secondly, a wide range of different exercise protocols has been used. Only high intensity, or long duration, exercise appears to lead to a large enough increase in free radical production to overwhelm the antioxidant defences [14,15,18]. Lovlin et al. [14], for example, demonstrated that exhaustive treadmill running increased levels of malondialdehyde, whereas running at a moderate intensity (70% $\dot{V}O_2$max) failed to produce this effect, and low intensity running (40% $\dot{V}O_2$max) even decreased this marker of oxidative stress. Some products of oxidative reactions may not be elevated directly after exercise, and reach their maximal levels only hours [9,28] or even days [19] after the end of exercise. Therefore, the absence of signs of oxidative stress directly after exercise does not necessarily imply that oxidative damage has not occurred.

Does exercise-induced oxidative stress affect sporting performance?

It is widely assumed that oxidative stress is detrimental to exercise performance, but there is little experimental evidence to support this. In animal studies, it has been shown that adding exogenous XOD to generate free radicals can damage muscle function [29] and that antioxidant supplementation can attenuate fatigue [30,31]. However, although antioxidant supplementation has been shown to decrease exercise-induced oxidative stress in humans [11,13], there is no convincing experimental evidence that this is accompanied by an increase in exercise performance in healthy human subjects [32–36]. It seems reasonable to assume that if oxidative stress had a major detrimental effect on exercise performance, antioxidant supplementation should have the potential to produce an ergogenic effect. The lack of such an effect suggests that exercise-induced oxidative stress has only minor effects on performance in the short term; long-term effects on health should not be so readily dismissed however, given the range of diseases that are associated with enhanced free radical production [4,37]. On the other hand, the increase in oxidative stress during exercise may signal an increase in antioxidant defences that protects against a wide range of oxidative stresses. Exercise may be good for you, at least when you stop.

Haemoglobin and myoglobin: a new source of exercise-induced oxidative stress?

Studies in our laboratory have focused on the role of haem proteins in inducing oxidative stress. Haemoglobin and myoglobin have the ability to both generate primary ROS and enhance the reactivity of ROS generated by other pathways

$$Fe^{2+} + O_2 = Fe^{3+} + O_2^{\cdot -} \quad (2)$$

$$O_2^{\cdot -} + O_2^{\cdot -} + 2H^+ = H_2O_2 + O_2 \quad (3)$$

$$R + Fe^{3+} + H_2O_2 = R^{\cdot +} + Fe^{4+}{=}O^{2-} + H_2O \quad (4)$$

The auto-oxidation of oxyhaemoglobin and oxymyoglobin (eqn 2) leads to superoxide formation

(eqn 2) and subsequent peroxide formation (eqn 3). Peroxides can react with ferric haem proteins to form two strong oxidants, ferryl ($Fe^{4+}{=}O^{2-}$) iron and a protein bound free radical ($R^{\bullet+}$). Eqn (4) provides the basis for the catalytic activity of a range of enzymes [2] involved in the removal of ROS (e.g. catalase), generation of bactericidal oxidants (e.g. neutrophil myeloperoxidase) or biosynthesis (e.g. prostaglandin H synthase). However, these enzymes are designed to control the reactivity of the products in eqn (4) so as to use them only on appropriate substrates. Haemoglobin and myoglobin are not designed for this role and the ferryl iron and free radicals they produce can react with a range of biological materials, most noticeably in initiating lipid peroxidation [38]. The clinical importance of these reactions has been reviewed recently [39].

The haemoglobin auto-oxidation rate has an unusual 'bell-shaped' dependence on pO_2 [40,41]. Therefore, in contrast with the mitochondrial situation, ROS production from haemoglobin can increase with the decrease in capillary and venous blood pO_2 associated with exercise. We have shown that the combination of eqns (2)–(4) leads to the production of free radicals bound to haemoglobin in healthy human blood [42,43]. Whether this pathway is a significant source of ROS during high intensity exercise remains to be seen. However, we have recently detected a long-lived increase in ferric haemoglobin following downhill running, that is associated with a decrease in whole blood GSH (Figure 1). Superoxide production from haemoglobin may increase the ferric haem protein concentration (eqn 2) and deplete erythrocyte antioxidant defences.

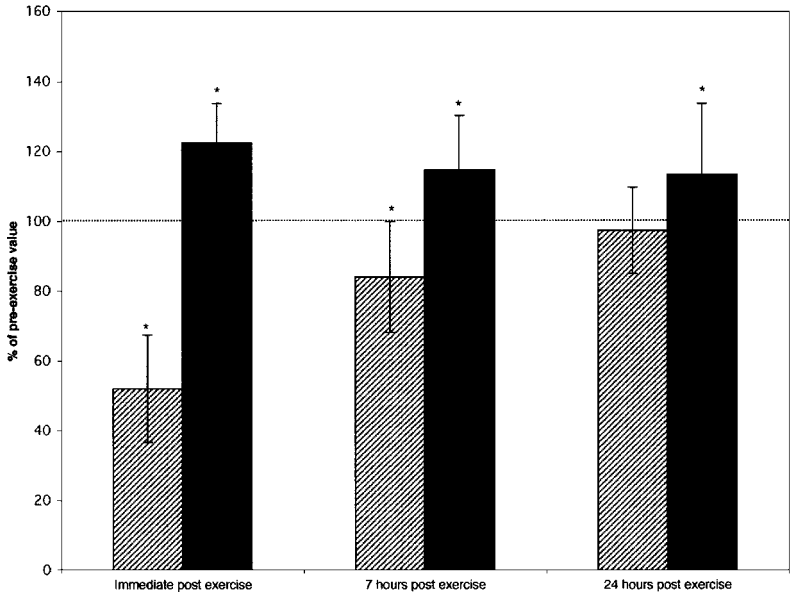
$$2GSH + H_2O_2 = GSSG + 2H_2O \qquad (5)$$

The clearest example of haem protein induced free radical damage comes from situations where the haem protein is removed from the environment of its antioxidant defences. In the absence of globin reductase enzymes the concentration of the reactive ferric species increases significantly. This is the case when haemoglobin-based blood substitutes are used extracellularly to improve oxygen delivery to patients [44]. It is particularly true of the disease rhabdomyolysis [45] which can be caused by a number of factors including exercise [46]. In the latter case muscle damage causes myoglobin release into the plasma. The myoglobin then accumulates in the kidneys. We have shown in an animal model that the myoglobin is in the ferric state in the kidneys [47]. Here it initiates lipid peroxidation and, in particular, the

Figure 1

Exercise effects on GSH and methaemoglobin levels

Changes in blood GSH (hatched bars) and methaemoglobin (black bars) levels following exercise. Six healthy non-smoking male runners completed 20 min of constant downhill running at 75% $\dot{V}O_2$max. Venous blood samples were taken pre-exercise, immediately post-exercise and after 7 and 24 h of recovery. Results are shown as the percentage of the pre-exercise value (±S.E.M.). * denotes a significant difference from pre-exercise value ($P < 0.05$).



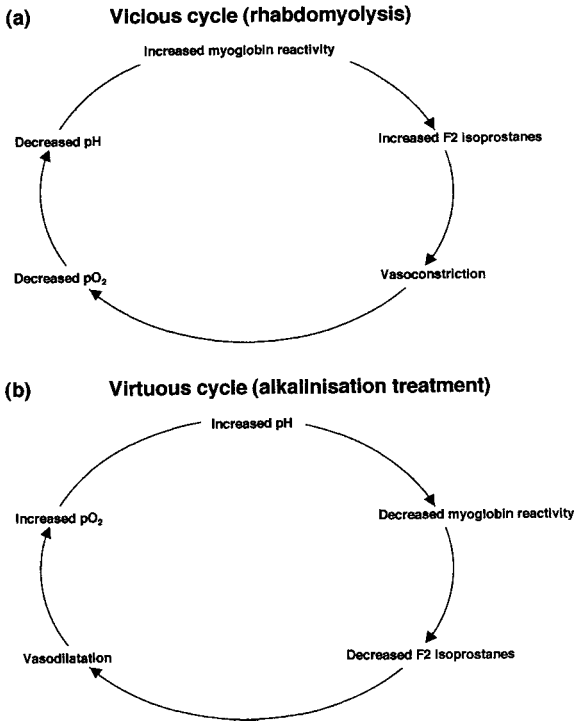
conversion of arachidonic acid into the vasoconstrictive F2-isoprostanes [48]. This results in a decrease in pO_2, leading to anaerobic glycolysis and a fall in tissue pH. Ferric myoglobin reactivity with peroxides is strongly enhanced at $pH < 7$ [38]. Therefore, once the F2-isoprostane levels rise above a critical level, a vicious cycle is set in motion, whereby a vasoconstrictor decreases the pH which, in turn, increases the concentration of the vasoconstrictor. One clinical treatment for rhabdomyolysis is alkalinization of the plasma. Increasing the pH may convert the 'vicious cycle' into a 'virtuous cycle' by decreasing myoglobin reactivity, decreasing F2-isoprostane levels, inducing vasodilatation and hence increasing oxygen delivery to the tissue [49]. This is turn would decrease anaerobic glycolysis and lactic acid production, raising tissue pH further (Figure 2).

We, and others, have shown that peroxide modifications of haem proteins lead to uniquely oxidatively modified proteins [50] that are not only *in vivo* markers for this form of damage, but are themselves more likely to initiate free radical damage [51]. These markers include the covalent binding of the haem prosthetic group to the polypeptide backbone. Whether these reactions occur in exercise that is less clearly detrimental than that leading to full blown rhabdomyolysis remains to be seen.

Figure 2

Possible mechanism of alkalinization treatment in preventing renal failure in rhabdomyolysis

See text for a description of these vicious and virtuous cycles.



Conclusion

High intensity exercise induces oxidative stress. There is no evidence that this affects sporting performance in the short term, although it may have longer term, not necessarily detrimental, health consequences. The mechanisms of exercise-induced oxidative stress are not well understood, though recent studies suggest that haem proteins may play an important role as initiators and transducers of free radical damage.

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References

1 Alderton, W. K., Cooper, C. E. and Knowles, R. G. (2001) Biochem. J. **357** 593–615
2 Cooper, C. E. (1994) in Free Radical Damage and its Control (Rice-Evans, C. A. and Burdon, R. H., eds.), pp. 65–109, Elsevier, Amsterdam
3 Halliwell, B. (1996) Biochem. Soc. Trans **24**, 1023–1027
4 Packer, L. (1997) J. Sports Sci. **15**, 353–363
5 Sjodin, B., Hellsten Westing, Y. and Apple, F. S. (1990) Sports Med. **10**, 236–254
6 Ji, L. L. (1999) Proc. Soc. Exp. Biol. Med. **222**, 283–292
7 Zhang, L., Yu, L. and Yu, C. A. (1998) J. Biol. Chem. **273**, 33972–33976
8 Demin, O. V., Kholodenko, B. N. and Skulachev, V. P. (1998) Mol. Cell. Biochem. **184**, 21–33
9 Koyama, K., Kaya, M., Ishigaki, T., Tsujita, J., Hori, S., Seino, T. and Kasugai, A. (1999) Eur. J. Appl. Physiol. Occup. Physiol. **80**, 28–33
10 Vina, J., Gimeno, A., Sastre, J., Desco, C., Asensi, M., Pallardo, F. V., Cuesta, A., Ferrero, J. A., Terada, L. S. and Repine, J. E. (2000) IUBMB Life **49**, 539–544
11 Dillard, C. J., Litov, R. E., Savin, W. M., Dumelin, E. E. and Tappel, A. L. (1978) J. Appl. Physiol. **45**, 927–932
12 Ashton, T., Rowlands, C. C., Jones, E., Young, I. S., Jackson, S. K., Davies, B. and Peters, J. R. (1998) Eur. J. Appl. Physiol. Occup. Physiol. **77**, 498–502
13 Ashton, T., Young, I. S., Peters, J. R., Jones, E., Jackson, S. K., Davies, B. and Rowlands, C. C. (1999) J. Appl. Physiol. **87** 2032–2036
14 Lovlin, R., Cottle, W., Pyke, I., Kavanagh, M. and Belcastro, A. N. (1987) Eur. J. Appl. Physiol. Occup. Physiol. **56**, 313–316
15 Niess, A. M., Hartmann, A., Grunert-Fuchs, M., Poch, B. and Speit, G. (1996) Int. J. Sports Med. **17**, 397–403
16 Kanter, M. M., Lesmes, G. R., Kaminsky, L. A., La Ham-Saeger, J. and Nequin, N. D. (1988) Eur. J. Appl. Physiol. Occup. Physiol. **57**, 60–63

17 Alessio, H. M., Hagerman, A. E., Fulkerson, B. K., Ambrose, J., Rice, R. E. and Wiley, R. L. (2000) Med. Sci. Sports Exerc. **32**, 1576–1581
18 Poulsen, H. E., Loft, S. and Vistisen, K. (1996) J. Sports Sci. **14**, 343–346
19 Hartmann, A., Pfuhler, S., Dennog, C., Germadnik, D., Pilger, A. and Speit, G. (1998) Free Radic. Biol. Med. **24**, 245–251
20 Dufaux, B., Heine, O., Kothe, A., Prinz, U. and Rost, R. (1997) Int. J. Sports Med. **18**, 89–93
21 Viguie, C. A., Frei, B., Shigenaga, M. K., Ames, B. N., Packer, L. and Brooks, G. A. (1993) J. Appl. Physiol. **75**, 566–572
22 Gleeson, M., Robertson, J. D. and Maughan, R. J. (1987) Clin. Sci. **73**, 501–505
23 Duthie, G. G., Robertson, J. D., Maughan, R. J. and Morrice, P. C. (1990) Arch. Biochem. Biophys. **282**, 78–83
24 Pincemail, J., Deby, C., Camus, G., Pirnay, F., Bouchez, R., Massaux, L. and Goutier, R. (1988) Eur. J. Appl. Physiol. Occup. Physiol. **57**, 189–191
25 Inoue, T., Mu, Z., Sumikawa, K., Adachi, K. and Okochi, T. (1993) Jpn. J. Cancer Res. **84**, 720–725
26 Margaritis, I., Tessier, F., Richard, M. J. and Marconnet, P. (1997) Int. J. Sports Med. **18**, 186–190
27 Witt, E. H., Reznick, A. Z., Viguie, C. A., Starke-Reed, P. and Packer, L. (1992) J. Nutr. **122**, 766–773
28 Maughan, R. J., Donnelly, A. E., Gleeson, M., Whiting, P. H., Walker, K. A. and Clough, P. J. (1989) Muscle Nerve **12**, 332–336
29 Barclay, J. K. and Hansel, M. (1991) Can. J. Physiol. Pharmacol. **69**, 279–284
30 Novelli, G. P., Falsini, S. and Bracciotti, G. (1991) Pharmacol. Res. **23**, 149–155
31 Shindoh, C., DiMarco, A., Thomas, A., Manubay, P. and Supinski, G. (1990) J. Appl. Physiol. **68**, 2107–2113
32 Malm, C., Svensson, M., Ekblom, B. and Sjodin, B. (1997) Acta Physiol. Scand. **161**, 379–384
33 Rokitzki, L., Logemann, E., Huber, G., Keck, E. and Keul, J. (1994) Int. J. Sport Nutr. **4**, 253–264
34 Snider, I. P., Bazzarre, T. L., Murdoch, S. D. and Goldfarb, A. (1992) Int. J. Sport Nutr. **2**, 272–286
35 Laaksonen, R., Fogelholm, M., Himberg, J. J., Laakso, J. and Salorinne, Y. (1995) Eur. J. Appl. Physiol. Occup. Physiol. **72**, 95–100
36 Itoh, H., Ohkuwa, T., Yamazaki, Y., Shimoda, T., Wakayama, A., Tamura, S., Yamamoto, T., Sato, Y. and Miyamura, M. (2000) Int. J. Sports Med. **21**, 369–374
37 Gutteridge, J. M. (1993) Free Radic. Res. Commun. **19**, 141–158
38 Reeder, B. J. and Wilson, M. T. (2001) Free Radic. Biol. Med. **30**, 1311–1318
39 Alayash, A. I., Patel, R. P. and Cashon, R. E. (2001) Antioxid. Redox Signal. **3**, 313–327
40 Balagopalakrishna, C., Manoharan, P. T., Abugo, O. O. and Rifkind, J. M. (1996) Biochemistry **35**, 6393–6398
41 Brooks, J. (1935) Proc. R. Soc. London Ser. B **118**, 560–577
42 Svistunenko, D. A., Patel, R. P., Voloshchenko, S. V. and Wilson, M. T. (1997) J. Biol. Chem. **272**, 7114–7121
43 Svistunenko, D. A., Davies, N. A., Wilson, M. T., Stidwill, R. P., Singer, M. and Cooper, C. E. (1997) J. Chem. Soc. Perkin Trans. II **2**, 2539–2543
44 Faivre, B., Menu, P., Labrude, P. and Vigneron, C. (1998) Artif. Cells Blood Substit. Immobil. Biotechnol. **26**, 17–26
45 Holt, S. G. R. (1999) in Critical Care Focus, vol, 1: Renal Failure (Galley, H. F., ed.), pp. 15–20, BMJ Books/Intensive Care Society, London
46 O'Donnell, J. and Gleeson, A. P. (1998) Eur. J. Emerg. Med. **5**, 325–326
47 Moore, K. P., Holt, S., Patel, R. P., Svistunenko, D. A., Zackert, W., Goodier, D., Reeder, B. J., Clozel, M., Anand, R., Cooper, C. E. et al. (1998) J. Biol. Chem. **273**, 31731–31737
48 Holt, S., Reeder, B., Wilson, M., Harvey, S., Morrow, J. D., Roberts, II, L. J. and Moore, K. (1999) Lancet **353**, 1241
49 Holt, S. and Moore, K. (2000) Exp. Nephrol **8**, 72–76
50 Reeder, B. J., Wilson, M. T., Holt, S. and Moore, K. (2002) Biochemistry **4**, 367–375
51 Osawa, Y. and Williams, M. S. (1996) Free Radic. Biol. Med. **21**, 35–41

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Gene expression in skeletal muscle

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Abstract

Muscle has an intrinsic ability to change its mass and phenotype in response to activity. This process involves quantitative and qualitative changes in gene expression, including that of the myosin heavy chain isogenes that encode different types of molecular motors. This, and the differential expression of metabolic genes, results in altered fatigue resistance and power output. The regulation of muscle mass involves autocrine as well as systemic factors. We have cloned the cDNAs of local and systemic isoforms of insulin-like growth factor-I (IGF-I) from exercised muscle. Although different isoforms are derived from the IGF-I gene

Key words: exercise, fibre type, IGF-I, local and systemic regulation, mechano growth factor (MGF).
Abbreviations used: *hc* gene, heavy chain gene; IGF-I, insulin-like growth factor-I; MGF, mechano growth factor.
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