Acute vs. chronic hypoxia: What are the consequences for skeletal muscle mass?

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Abstract

Hypoxia is a state of lowered oxygen tension that can be created by environmental or pathological conditions. Regardless the origin of hypoxia, skeletal muscle cells adapt to deal with the acute or chronic reduction in oxygen availability. Although contrasting results have been reported as well, long lasting hypoxia generally leads to a negative regulation of protein balance and a loss of muscle mass, whereas intermittent hypoxia seems rather to exert a positive effect on muscle growth in the context of resistance exercise training. The purpose of the present review is to present the idea that chronic and acute hypoxia regulate skeletal muscle mass in two opposite ways. Chronic hypoxia-induced muscle atrophy in native highlanders, climbers or patients suffering from chronic obstructive pulmonary disease was previously thought to be caused by less calories ingested and reduced physical activity. More and more evidence is accumulating showing that hypoxia itself contributes to the loss of muscle mass during chronic exposure. In contrast repeated acute hypoxic sessions have the potential to slow down muscle atrophy and even to stimulate muscle mass accretion when coupled to resistance exercise as is the case with occlusion training. Further investigation should now focus on the molecular mechanisms by which acute and chronic hypoxia regulate skeletal muscle mass. Particular attention should be paid to satellite cells, which can be activated by hypoxia *in-vitro*.

Citation: Deldicque L, Francaux M (2013) Acute vs. chronic hypoxia: What are the consequences for skeletal muscle mass? Cellular and Molecular Exercise Physiology 2(1): e5 doi: 10.7457/cmep.v2i1.e5

Editor: Adam Sharples PhD.
Received: Oct 1st, 2013; **Accepted:** Oct 29th, 2013; **Published:** Nov 14th, 2013

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Hypoxia is a state of low oxygen tension (PO_2) created either by environmental conditions like high altitude exposure, or by pathological conditions such as chronic obstructive pulmonary disease (Baldi et al., 2010), obstructive sleep apnea (Garvey et al., 2009) or severe anemia (Grocott et al., 2007). During exercise, hypoxia can also occur, but contrary to the previous situations, oxygen restriction is in this case limited to skeletal muscle (Richardson et al., 2001). Regardless of the origin of hypoxia, skeletal muscle cells adapt to deal with acute or chronic reduction in oxygen availability. For example, patients exposed to chronic hypoxemia due to lung disease show muscle wasting and a higher 5 yr mortality rate (Schols et al., 2005). Several studies have also revealed that highlanders and hikers undergo reductions in muscle fiber cross sectional area (Hoppeler et al., 1990; MacDougall et al., 1991; Mizuno et al., 2008). Although contrasting results have been reported as well (Green et al., 2000; Lundby et al., 2004), long lasting hypoxia generally leads to a negative regulation of protein metabolism and a loss of muscle mass whereas acute hypoxia seems to rather exert a positive effect on protein balance in human (D'Hulst et al., 2013; Nishimura et al., 2010; Loenneke et al., 2012).

The purpose of this review is to present the idea that chronic and acute hypoxia regulate skeletal muscle mass in two distinct ways (Fig. 1). This hypothesis is based on the recent literature, although not in an exhaustive way, which was beyond the aim of the present manuscript. Before developing this idea further, the concepts of chronic and acute hypoxia must be defined. The term “chronic hypoxia” will be used for hypoxic conditions lasting for several days, whereas “acute hypoxia” will be used for a period of several hours. Another important point to rise initially is the difference between normobaric and hypobaric hypoxia. Extrapolating the results obtained in normobaric hypoxic chambers to altitude situations must be done with caution because hypobaric hypoxia seems to be a more severe environmental condition than normobaric hypoxia (Millet et al., 2012). However, the regulation of protein metabolism has not been compared under both conditions. Therefore, it is currently difficult to know whether hypobaric hypoxia affects muscle mass more than normobaric hypoxia. Importantly, ambient hypoxia reduces skeletal muscle oxygenation, which could contribute to the activation of intracellular signaling leading to a deregulation of balance between protein synthesis and protein breakdown. Exposition to hypoxia (FiO_2 10%) has been shown to reduce skeletal muscle oxygen tension from ~50mmHg to ~20mmHg in mice (Reinke et al., 2011) and from ~35mmHg to ~25mmHg in human (Richardson et al., 2006). Definitely, if the enhancement of protein balance by acute hypoxia exposure is confirmed by future studies, resistance exercise performed in conditions of reduced oxygen availability could become extremely useful not only for athletes looking for an improvement of performance due to increased muscle mass, but also for patients suffering from muscle wasting.

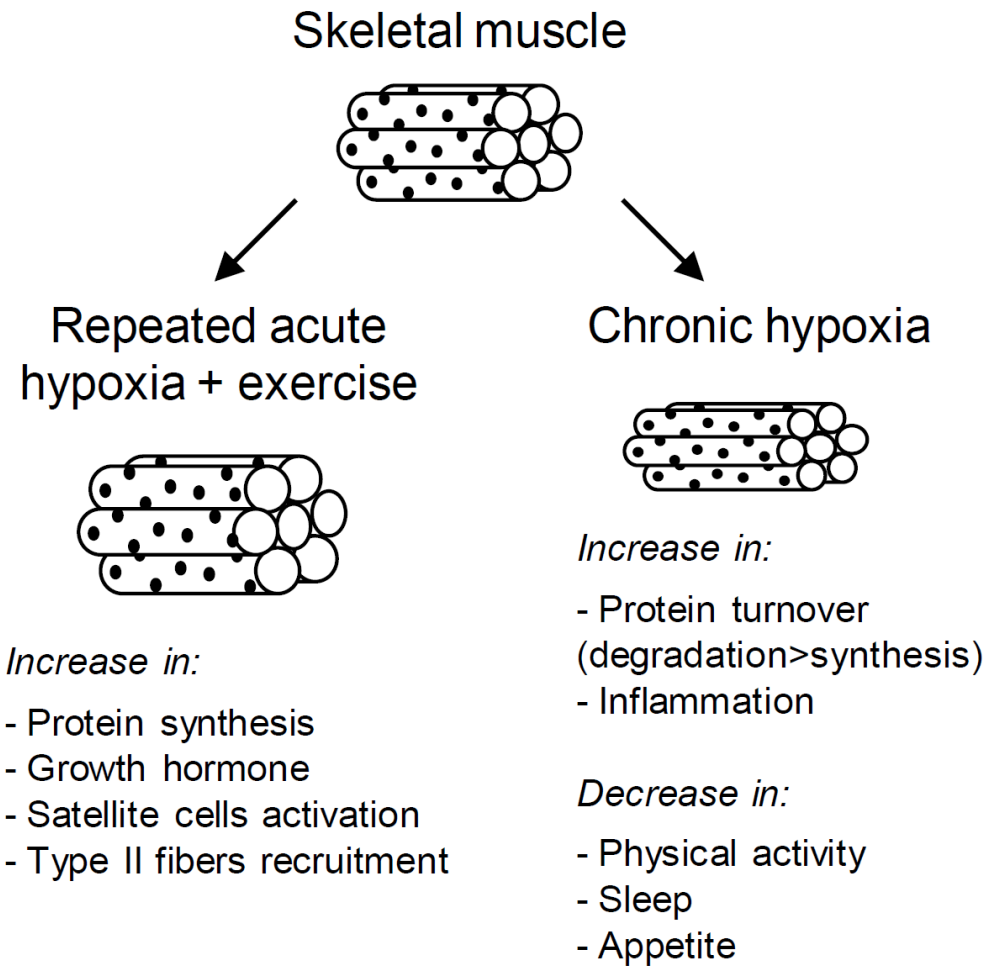

Figure 1. Regulation of muscle mass by acute and chronic hypoxia. Protein turnover is increased during chronic hypoxia, with protein breakdown being elevated to a greater extent than protein synthesis, resulting in a loss of muscle mass. In addition, an increase in inflammation and a decrease in physical activity, sleep duration/quality and appetite may all contribute to the catabolic state observed during chronic hypoxia. In contrast acute hypoxic sessions have the potential to slow down muscle atrophy and even to stimulate muscle mass accretion when coupled with resistance exercise possibly by increasing growth hormone production and satellite cell activation.

Chronic hypoxia: Native highlanders and high altitude climbers

Reduction in muscle mass is a common feature of native highlanders residing at altitude (Fiori et al., 2000), lowlanders exposed to low atmospheric oxygen conditions for more than 3 weeks (Rose et al., 1988), and patients suffering from lung diseases (Schols et al., 2005). The first studies looking at muscle atrophy during chronic hypoxia were performed in climbers after a Himalayan expedition above 5000m for 8 weeks (Hoppeler et al., 1990) and in experimental subjects after 40 days exposure to hypoxia in a hypobaric chamber (MacDougall et al., 1991). Hypoxic exposure was associated with skeletal muscle atrophy, and increased capillary density, which may support a more favorable oxygen transport to the muscle cells by decreasing the diffusion distance between blood and mitochondria. While muscle atrophy could be a consequence of hypoxic exposure per se, very high altitude expeditions are also associated with reduction in appetite, sleep deprivation. Also in low temperatures (Kayser, 1994), and in hypobaric chambers the limited space available may be associated with detraining atrophy. Thus, it is unclear whether muscle atrophy and the increase in capillary density are caused by hypoxia or by confounding factors. For example, a 21-day expedition to Mont Denali, did not induce any significant change in mean muscle fiber area (Green et al., 2000). Those results were confirmed in active Danish subjects exposed to 4100m for 8 weeks in the surroundings of La Paz in Bolivia (Lundby et al., 2004). It is thus tempting to state that a certain level of physical activity is critical in maintaining muscle mass under moderate hypoxia. To test this hypothesis, skeletal muscle adaptations were studied in very active climbers as well as in less active staff members at the base camp of Mount Everest at 5250m. Because the fiber size decreased to the same extent in both groups, the authors concluded that high altitude-associated weight loss is mainly the result of muscle fiber atrophy and that muscle wasting is independent of activity level (Mizuno et al., 2008). While muscle fiber atrophy at altitude above 4500m seems unavoidable (Hoppeler et al., 1990;MacDougall et al., 1991;Mizuno et al., 2008), muscle fiber area can be preserved at lower altitudes if physical activity and diet are properly maintained (Green et al., 2000;Lundby et al., 2004).

The mechanisms regulating muscle mass in humans during long-term expeditions at high altitude are still poorly understood, but recent animal studies give further insight into the anabolic and catabolic processes in response to chronic hypoxic conditions *in-vivo* (Chaillou et al., 2012;Chaudhary et al., 2012;Chaillou et al., 2013a;Favier et al., 2010). Male rats exposed for several days to hypobaric hypoxia (7620m) lost up to 30% of muscle mass (Chaudhary et al., 2012). This was associated with a higher protein turnover assessed by an increase of both protein synthesis and degradation. However, the increase in protein degradation was much higher than

protein synthesis (5-fold vs 1.5-fold), resulting in skeletal muscle loss. In another study wherein male rats were exposed to hypobaric hypoxia (6300m) for 3 weeks, muscle mass was decreased by about 15%. Considering the decreased muscle mass in a pair-fed group exposed to normoxia, the authors concluded that 60% of the muscle loss observed in hypoxia was independent of hypophagia (Favier et al., 2010). This observation was also in good agreement with previous data showing that increasing dietary protein intakes in rats is not able to reduce muscle loss related to high altitude exposure (Bigard et al., 1996). Favier et al. (2010) showed also that the decrease in muscle mass was accompanied by a marked increase in regulated in development and DNA damage responses (REDD1) expression and a down-regulation of the protein kinase B (PKB)/mechanistic target of rapamycin complex 1 (mTORC1) pathway, a key regulatory pathway of protein synthesis. Compared to male rats, females are more resistant to hypoxia (Wood and Stabenau, 1998) and are able to keep muscle mass unchanged after 8 weeks exposure to hypobaric hypoxia (5500m) (Chaillou et al., 2012). Still, hypoxia impaired partially and transiently the increase in plantaris muscle mass induced by removing the soleus and the gastrocnemius muscles as well as the increase in mTOR, ribosomal protein S6 kinase 1 (S6K1) and ribosomal protein S6 phosphorylations (Chaillou et al., 2012). The repression of the PKB/mTOR pathway by hypoxia observed by Favier et al. (2010) and Chaillou et al. (2012) contrasts with the activation of protein synthesis measured by Chaudhary et al. (2012). At least two hypotheses may explain this apparent discrepancy: 1) Protein synthesis could be activated after a few days exposure to hypoxia (Chaudhary et al., 2012) and inhibited after several weeks (Chaillou et al., 2012; Favier et al., 2010); 2) indirect markers do not always reflect how protein synthesis is actually modified (Greenhaff et al., 2008).

Although not corroborated by everyone (Favier et al., 2010), chronic hypoxia seems to activate the ubiquitin-proteasome pathway as well as the calpains in rats (Chaillou et al., 2012; Chaudhary et al., 2012). The mRNA level of the two muscle-specific ligases muscle ring finger protein-1 (MuRF-1) and muscle atrophy F box (MAFbx) (Chaillou et al., 2012) and the level of ubiquitinated proteins (Chaudhary et al., 2012) were increased after several days of exposure to hypoxia in rat skeletal muscle. Beside the ubiquitin-proteasome pathway and calpains, attention in a third proteolytic system, i.e. the autophagy-lysosomal pathway, was increasing (Tanida, 2011; Bonaldo and Sandri, 2013). The ubiquitin-proteasome pathway and autophagy-lysosomal pathway are under control of, amongst others, the forkhead box protein O (FoxO) transcription factors, which themselves are regulated by PKB. Whereas autophagy clearly plays an important role in skeletal muscle degradation, this process has only been investigated indirectly in skeletal muscle during hypoxia via lipofuscin release, which reflects membrane damage (Martinelli et al., 1990).

Using two-dimensional difference in gel electrophoresis and mass spectrometry techniques, De Palma investigated hypoxia-induced changes in rat skeletal muscle (De Palma et al., 2007). Hypoxia-inducible factor 1 alpha (HIF-1α), a master regulator of the hypoxic response (Semenza, 2011), and pyruvate dehydrogenase kinase 1 (PDK1) expression was up-regulated after 2-week normobaric hypoxia (FiO_2 10%) whereas no modification of total mTOR was observed. Those results contrast with data obtained with a similar protocol and the same analytical techniques in humans where a slight decrease in total mTOR was found after 7-9 days at 4559m without any change in HIF-1α and PDK1 (Vigano et al., 2008). Only one study measured the protein synthesis and degradation rates after several days of adaptation to hypoxia (Holm et al., 2010). At rest, the whole body degradation rate was higher at 4559m altitude compared to sea level, but the synthetic rate remained similar. Interestingly, at the muscle level, the myofibrillar fractional synthetic rate was elevated by high altitude-induced hypoxia whereas the sarcoplasmic subfraction remained unaffected (Holm et al., 2010). In addition to activate HIF-1α, hypoxia could induce some physiological adaptations via an increase in reactive oxygen species (Clanton, 2007), although this is still controversial (Clanton, 2005). As reactive oxygen species contribute to muscle disuse atrophy (Powers et al., 2005), it would be worth to further investigate whether reactive oxygen species mediate hypoxia-induced muscle loss.

All together those results show that chronic hypoxia induces muscle atrophy preferentially by accelerating protein degradation in healthy people (Table 1). In some cases, protein synthesis, and more particularly the myofibrillar fraction, can be increased too, leading to a higher protein turnover. However, the increase in protein degradation being much higher than the increase in protein synthesis, protein balance is negative during chronic hypoxia, which can lead to muscle loss over time.

Chronic obstructive pulmonary disease

Several interesting parallels and differences exist between chronic exposure to high altitude in healthy humans and chronic hypoxia in chronic obstructive pulmonary disease (COPD) patients (Raguso et al., 2004). Both may induce a decreased physical fitness, a loss of appetite, an increased oxidative stress and an increased production of cytokines, all factors known to favor a negative net protein balance. Whole skeletal muscle cross-sectional area is ~25% lower in patients with COPD than in control subjects (Bernard et al., 1998), often due to a decrease in fiber cross-sectional area (Jagoe and Engelen, 2003). This decrease in cross-sectional area affects mainly type II fibers (Whittom et al., 1998) although type I cross-sectional area may be affected as well (Gosker et al., 2002). In contrast to muscle of native highlanders or high altitude climbers, in which increased capillary density is observed (Hoppeler et al., 1990), in COPD patients the reduced muscle mass is not counterbalanced by a preservation of muscle capillaries (Jobin et al., 1998).

In COPD patients, it is generally assumed that the balance is tilted toward reduced protein synthesis and enhanced protein degradation (Hussain and Sandri, 2013). However the precise mechanisms underlying this imbalance remain unclear. Activation of catabolic factors such as interleukin-6 and cortisol and inhibition of anabolic factors such as testosterone, dehydroepiandrosterone, and insulin-like growth factor I could be involved (Debigare et al., 2003). In addition, local factors, such as oxidative stress caused by increased reactive oxygen species, or systemic factors, such as; inflammation, malnutrition, corticosteroid therapy, inactivity, smoking, aging, and hypoxemia could contribute to muscle atrophy in COPD patients (Debigare et al., 2001).

Well-known anabolic and catabolic signaling pathways were screened in skeletal muscle of COPD patients (Plant et al., 2010). Compared to control individuals, skeletal muscle of COPD patients displayed an increase in MAFbx and neural precursor cell expressed developmentally down-regulated protein 4 (Nedd4), two ligases regulating ubiquitin-mediated protein degradation. However, myostatin, a negative regulator of muscle growth, MuRF-1 and the myogenic regulatory factors Myf5, myogenin, and MyoD were not differentially expressed. There were no differences in the level of phosphorylation of PKB, glycogen synthase kinase 3 beta (GSK3β), S6K1, inhibitor of nuclear factor-kappa B (NF-κB) alpha (IκBα), NF-κBp65 or NF-κBp50, or gene expression of beclin-1 or microtubule- associated protein 1

Table 1. Effect of chronic and acute hypoxia on protein metabolism in human skeletal muscle.

	Protein synthesis	Protein breakdown	Net protein balance
Chronic hypoxia			
High altitude	↗ or ~	↗↗	Negative
COPD	↘	↗	Negative
Acute hypoxia			
Single exposure	↘ or ~	?	?
Single exposure + ex	↘ (Etheridge, 2011) or ↗ (Imoberdorf, 2006)	?	?
Repeated exposure + ex	↗	?	Positive

COPD, chronic obstructive pulmonary disease; ex, exercise; ↘, decrease; ↗ increase; ? unknown or understudied.

light chain (LC3), suggesting that PKB signaling was not down-regulated and the NF-κB inflammatory pathway and autophagy were not activated in skeletal muscle of COPD patients. Therefore muscle atrophy associated with COPD seems to result from the recruitment of specific regulators of ubiquitin-mediated proteolytic pathways and inhibition of muscle growth (Plant et al., 2010). Although the relative contribution of hypoxia per se to those mechanisms is quite difficult to evaluate, comparing hypoxemic to non hypoxemic COPD patients may help to partially answer this issue. Compared to non hypoxemic COPD patients (PaO_2 73 mmHg), hypoxemic patients (PaO_2 54 mmHg) presented a substantial decrease in phosphorylation of several intermediates of the PKB/mTORC1 pathway in skeletal muscle (Favier et al., 2010). These findings highlight the role of hypoxia per se in the down-regulation of an important regulatory pathway of protein synthesis. Whereas high altitude and COPD clearly lead to skeletal muscle wasting, it has long been unknown whether hypoxia per se contributed to this phenomenon. Based on the current literature, more and more evidence indicate that it is indeed the case. In addition, muscle loss can be aggravated by nutritional deficit, reduction in physical activity, inflammation and/or oxidative stress.

Acute hypoxia: Hypoxia *in-vitro*

In-vitro, it is commonly assumed that acute hypoxia inhibits muscle protein synthesis (Koumenis and Wouters, 2006) primarily by inhibiting mTORC1 via activation of the AMP-activated protein kinase (AMPK) (Liu et al., 2006) and increased expression of REDD1 (Brugarolas et al., 2004). Endoplasmic reticulum (ER) stress and its downstream response, the unfolded protein response, is another mechanism that has recently been proposed to participate in the reduction of protein synthesis under hypoxia (Koritzinsky et al., 2006). *In-vitro*, hypoxia activates HIF-1α more consistently than *in-vivo*, probably because of the very high level of hypoxia used in cell cultures (0-2% O_2). However, it is unknown whether HIF-1α is directly responsible for the decrease in protein synthesis observed in vitro as HIF-1α and the mTORC1 pathway have been shown to regulate each other (Greer et al., 2012;Lee et al., 2009;Cam et al., 2010). On the other hand, hypoxia has also been shown to inhibit mTORC1 in a HIF-1α-independent way in cell cultures (Arsham et al., 2003). Whether these observations from cell cultures, where very low concentrations of oxygen are used, may be extrapolated to living organisms remains an open question. In addition, the standard conditions in which cells are usually grown (21% O_2) should be considered as hyperoxic. Indeed, oxygen tension in human skeletal muscle approximates 30-40 mmHg in normoxia (Richardson et al., 2006), which corresponds roughly to 5% O_2 in cell culture. Therefore oxygen concentration should be lowered to ~5% to get physiological normoxic conditions. As a result, oxygen concentrations below 5% represent hypoxic conditions.

Single exposure to hypoxia

The results reported *in-vivo* and more particularly in human are less clear. Compared to normoxic conditions, breathing normobaric hypoxic air (FiO_2 12%) in a post-absorptive state did not modify muscle protein synthesis at rest but blunted the increase in protein synthesis induced by exercise (Etheridge et al., 2011). Contrary to the observations *in-vitro*, the blockade seemed independent of the mTORC1 pathway since hypoxia did not modify the phosphorylation of S6K1 or the expression of REDD1 both at rest and after exercise (Etheridge et al., 2011). The combined effects of hypoxia and exercise were also studied via an original experimental design wherein a group of subjects climbed from 550m to 4559m by foot and another group was flown by helicopter (Imoberdorf et al., 2006). Muscle protein synthesis rate was measured in both groups at sea level and at altitude. In the air group, the rate of synthesis was not modified, whereas in the foot group, a 35%-increase in protein synthesis was measured 19-23hrs after the end of the exercise, suggesting that exercise is still able to activate muscle protein synthesis even in hypoxia, contrary to the findings of Etheridge et al. (2011). Both studies used similar techniques for measuring protein synthesis, in both studies the subjects were in a fasted state when the protein synthesis measurements were made and the levels of hypoxia were similar. The major difference is probably the timing of measurements after the beginning of exposure to hypoxia. In the study of Etheridge et al. (2011), the measure was made between the first and the third hour after the beginning of exposure to hypoxia whereas in the sudy of Imoberdorf et al. (2006) after one day at altitude. Conjointly, these results seem to indicate that exercise-induced protein synthesis could be rapidly decreased at the onset of hypoxic exposure and restored after one day. This hypothesis however should be verified experimentally.

To the best of our knowledge, the study of D'Hulst et al. (2013) from our lab is the first to have systematically studied the effect of acute hypoxia (FiO_2 11%) on anabolic and catabolic signalling pathways in human skeletal muscle at rest. Whereas markers of protein degradation were only marginally enhanced, PKB and S6K1 phosphorylation were higher in skeletal muscles of subjects exposed for 4h to normobaric hypoxia. Interestingly,

despite a decrease in blood SpO_2 and tissue oxygenation index measured by near-infrared spectroscopy, HIF-1α expression remained unaltered at both the protein and mRNA level (D'Hulst et al., 2013). The latter suggested that other, perhaps systemic factors, were involved in the activation of intramuscular signaling. Two likely candidates are insulin and cortisol, previously shown to be altered during hypoxic exposure (Larsen et al., 1997). Whereas plasma cortisol concentration was not modified by hypoxia, insulin returned more slowly to basal level after a standardised breakfast in the hypoxic trial. Independently of an increase in glucose concentration, insulin was 2 fold higher at the end of the exposure to environmental hypoxia and could partially explain several observations we made at this time, i.e. higher phosphorylation of PKB and S6K1. Although we did not measure plasma catecholamines concentrations, it is possible that adrenaline contributed to the increase in insulin as adrenaline increases at high altitude (Mazzeo et al., 1994) and it regulates insulin secretion by the pancreas (Lacey et al., 1993). If high concentrations of adrenaline inhibit insulin secretion, *in-vitro* studies showed that low concentrations (10 nmol/l) potentiate glucose-induced insulin secretion by isolated human islets of Langerhans (Lacey et al., 1993). Those concentrations correspond to physiological plasma levels reached after one-day exposure to ~4300m altitude (Mazzeo et al., 1994). Nevertheless, the activation of insulin secretion by adrenaline observed in vitro was transitory and followed by a sustained inhibition of secretion (Lacey et al., 1993). Therefore, adrenaline could participate to the increase in plasma insulin levels in the first hours of exposure to hypoxia but other regulatory signals probably overrule the long-term inhibitory effect of adrenaline on insulin secretion. Indeed, the hypoxia-induced increase in insulin persists for several days, thereafter (15-21 days) the concentration returns to sea level values (Sawhney et al., 1991).

In another study undertaken by our lab insulin concentrations were not modified during exposure to hypoxia (FiO_2 11%), probably because of a different nutritional pattern and/or exposure duration, the phosphorylation of PKB and S6K1 was not different between normoxia and hypoxia (unpublished results). These observations reinforce the idea that insulin is likely a main mediator of acute hypoxia-induced phosphorylation of the PKB pathway. Whether the activation of the PKB signaling pathway positively regulates protein synthesis during acute hypoxia is difficult to establish. Unfortunately, protein synthesis was not measured directly in D'Hulst et al. (2013) and the results available in the literature are inconclusive. Resting protein synthesis is either decreased (Rennie et al., 1983) or unchanged (Etheridge et al., 2011; Imoberdorf et al., 2006) by acute hypoxia in humans, but never increased. This suggests that the increase in insulin concentration and the activation of the PKB signaling pathway are not sufficient to activate protein synthesis during acute exposure to hypoxia at rest. Clearly, data are lacking to determine whether the activation of the PKB signaling pathway induced by an acute exposure to hypoxia could be beneficial for protein synthesis while recovering in normoxia as it is the case in training programs based on repeated exposures to hypoxia.

Repeated acute exposure to hypoxia

One efficient way of creating local hypoxia is to use a cuff to restrict blood flow into the limbs. Occlusion training alone can limit muscle atrophy in case of muscle disuse and induce hypertrophy when coupled with resistance exercise (Loenneke et al., 2012). This can provide a unique beneficial mode of exercise in the clinical setting because it produces positive training adaptations, at an intensity equivalent to physical activity of daily life (10–30% of maximal work capacity) (Abe et al., 2006). Muscle hypertrophy has recently been shown to occur during exercise at an intensity as low as 20% of the one-repetition maximum (1-RM) together with moderate vascular occlusion (Sumide et al., 2009). Blood flow restriction training has been shown to be quite beneficial to athletes (Takarada et al., 2000a), patients in postoperative rehabilitation (Takarada et al., 2000b), cardiac rehabilitation patients (Takano et al., 2005), and the elderly (Abe et al., 2010). For detailed information on the topic, the reader is referred to a recent meta-analysis (Loenneke et al., 2012).

Physiologically, occlusion training results in several changes to the body, the main modification being local hypoxia. Metabolic by-product accumulation seems to be the primary mechanism underpinning the benefits seen with occlusion training. Whole blood lactate (Gentil et al., 2006;Takano et al., 2005), plasma lactate (Takano et al., 2005;Fujita et al., 2007), and muscle cell lactate (Kawada and Ishii, 2005;Kawada and Ishii, 2008) accumulation due to the restriction of blood flow results in increased growth hormone, which was previously shown to be stimulated by an acidic intramuscular environment (Takarada et al., 2000a). However, growth hormone does not necessarily lead to an accretion of muscle mass (Rennie, 2003). Evidence indicates that a low pH also stimulates sympathetic nerve activity through a chemoreceptive reflex mediated by intramuscular metaboreceptors and group III and IV afferent fibers (Victor and Seals, 1989). Kawada and Ishii (2008) found that 2 weeks of chronic occlusion in rats caused a fiber-type shift from slow to fast. They attributed this to the additional recruitment of large motor units and their associated type II fibers at the expense of rapid fatigue in slow oxidative fibers during blood flow restriction.

Recent studies have shown increased protein synthesis following acute bouts of blood flow restriction training, accompanied by higher phosphorylation of the PKB/mTOR pathway (Fujita et al., 2007; Fry et al., 2010). In addition, expression of the proteolysis-related genes FoxO3a, MAFbx and MuRF-1, as well as the negative regulator of muscle mass, myostatin, were decreased 8hrs after an acute exercise bout with blood flow restriction (Manini et al., 2011). Similarly a decrease in the mRNA level of myostatin and an increase in the mRNA level of follistatin isoforms, growth and differentiation factor-associated serum protein 1 and MAD-related protein could contribute to muscle hypertrophy after 8 weeks of low-intensity resistance exercise associated with moderate blood flow restriction (Laurentino et al., 2012). In contrast, mRNA expression of other myogenic- and proteolysis-related targets did not change or differ between occluded and non-occluded exercise conditions (Drummond et al., 2008;Manini et al., 2011).

Blood flow restriction training alone/combined with low-intensity resistance exercise has been developed originally to improve pathological states. This kind of training has proven its efficacy in reducing muscle atrophy or even to induce muscle hypertrophy but the degree of hypertrophy is less than the level obtained by athletes with classical high-intensity (>70% 1-RM) resistance training (Loenneke et al., 2012). However practicing high-intensity exercise while occlusion is applied is not conceivable. As hypoxia is thought to play a major role in adaptations induced by blood flow restriction (Drummond et al., 2008), it has been postulated that by placing the entire body in a hypoxic environment, such as a hypoxic chamber, muscle hypertrophy could be more efficiently and more broadly up-regulated than with local occlusion (Nishimura et al., 2010). This hypothesis has been recently tested and refuted as training at the same intensity while breathing hypoxic air or with blood flow restriction results in similar increases in muscle cross sectional area and strength (Manimmanakorn et al., 2013). The advantage of using a hypoxic room is that high-intensity resistance protocols can be applied. High-intensity (70% 1-RM) training induced more muscle hypertrophy in subjects who

trained for 6 weeks in a hypoxic chamber (FiO_2 16%, ~2000m) than those in normoxia without differences in rate of perceived exertion during training (Nishimura et al., 2010), contrary to blood flow restriction training (Loenneke et al., 2010). Muscle strength was significantly increased after 6 weeks of training in both normoxic and hypoxic groups but only in the hypoxic group after 3 weeks, suggesting that exposure to hypoxia accelerates the increase in muscle strength. Interestingly, muscle hypertrophy was not significant in the group exposed to hypoxia without exercising, indicating that hypoxia alone is insufficient to increase muscle strength or to induce muscle hypertrophy and that it must be combined with exercise to achieve these results (Nishimura et al., 2010). In addition, a threshold corresponding to ~4500m of altitude seems to exist above which hypoxia does not induce any superior hypertrophy following resistance training compared to normoxia (Friedmann et al., 2003). Definitely acute hypoxia induces different, if not opposite, muscle adaptations than chronic hypoxia. Anabolic signals are triggered by acute hypoxia such as insulin and growth hormone. However it is unknown whether they effectively contribute to the increase in muscle mass observed after repeated sessions of resistance exercise in hypoxia. Moreover, protein degradation has been neglected in acute hypoxia studies and deserves more attention in the future.

Satellite cell activity and hypoxia

In addition to protein turnover, cell turnover also participates to the regulation of muscle mass (Pallafacchina et al., 2012). Myonuclear accretion, i.e. increase in the number of myonuclei within the muscle fibers, takes place via proliferation and fusion of satellite cells, myogenic stem cells associated to skeletal muscle fibers and involved in muscle regeneration. Exercise is a well-known activator of satellite cells, and more particularly eccentric resistance exercise (Macaluso and Myburgh, 2012). On the contrary, satellite cells and myonuclei may undergo apoptosis during muscle atrophy. However, the later point is controversial and it is still debated whether myonuclear loss occurs in atrophying muscle.

In-vitro, acute hypoxia is able to activate proliferation (Chakravarthy et al., 2001; Csete et al., 2001; Koning et al., 2011; Urbani et al., 2012), to promote self-renewal (Liu et al., 2012) and to inhibit differentiation of satellite cells (Gustafsson et al., 2005; Liu et al., 2012; Majmundar et al., 2012), although conversely activation of differentiation has also been shown (Kook et al., 2008). Interestingly short-term low-load resistance exercise performed with partial blood flow restriction was shown to result in marked proliferation of myogenic stem cells and myonuclei addition in human skeletal muscle, which was accompanied by substantial myofibre hypertrophy (Nielsen et al., 2012). On the other hand, ambient hypoxia has been shown to reduce satellite cells activity and protein synthesis in rats, contributing to impaired formation and growth of new fibers and thereby to the accelerated muscle loss observed after extensive injury compared to normoxia (Chaillou et al., 2013b). Similar results have been found in skeletal muscle of climbers having stayed for 6 weeks above 5000m (Mancinelli et al., 2011). Satellite cells from muscle biopsies after high-altitude expedition showed a significantly lower ability to regenerate skeletal muscle probably due to reduced activity, decreased myogenicity and fusion ability. COPD patients with a reduced muscle mass have less centrally located nuclei as well as more senescent satellite cells than healthy subjects or patients with a preserved muscle mass (Theriault et al., 2012). These results suggest that an increase in damage/repair recurrence, possibly due to hypoxia, may exhaust the regenerative capacity of satellite cells in COPD patients with reduced muscle mass, leading to the senescence of satellite cells and muscle atrophy. The signaling pathways mediating the regulation of satellite cells in general are poorly described and even less is known about the regulation of satellite cells by hypoxia. Satellite cell activation is controlled by several growth factors, intracellular signaling pathways and transcription factors (Cassano et al., 2009) which preferentially regulate proliferation or differentiation of satellite cells. Insulin-like growth factor-1 is unique, in that it promotes both proliferation and differentiation. In contrast, satellite cell proliferation is impaired by inhibitory factors, such as myostatin and other transforming growth factor beta family members. The Notch and Wnt signaling pathways appear to have a major role in controlling the balance between satellite cell proliferation and differentiation (Brack et al., 2008). Whether hypoxia regulates the Notch pathway is controversial as some authors found increased activation (Gustafsson et al., 2005; Liu et al., 2012) and others no modification (Majmundar et al., 2012) under hypoxia. Gustafsson et al. (2005) propose a molecular model where HIF-1α and Notch intracellular domain form a point of convergence between the two signaling mechanisms, leading to stabilization of Notch intracellular domain, recruitment of HIF-1α to Notch-responsive promoters and activation of Notch downstream genes (Gustafsson et al., 2005). On the other hand, Majmundar et al. (2012) propose a mechanism involving the phosphatidylinositol 3-kinase/PKB pathway and independent of HIF-1α (Majmundar et al., 2012). The exact mechanisms by which hypoxia regulates satellite cells activation and differentiation are far to be elucidated and are probably a promising area of research.

Conclusion

Chronic hypoxia-induced muscle atrophy was previously thought to be caused by less calories ingested and reduced physical activity levels. More and more evidence accumulate showing that hypoxia itself contributes to the loss of muscle mass during chronic hypoxia. In contrast acute hypoxic sessions have the potential to slow down muscle atrophy and even to stimulate muscle mass accretion when coupled with resistance exercise. Further investigation should now focus on the molecular mechanisms by which acute and chronic hypoxia regulate skeletal muscle mass. Particular attention should be paid to satellite cells, which can be activated by hypoxia *in-vitro*.

Acknowledgments

MF is supported by the Ministry of Sports of the Wallonia-Brussels Federation of Belgium.

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