Special Review Series – Biogenesis and Physiological Adaptation of Mitochondria
Response of skeletal muscle mitochondria to hypoxia

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(The following extract is taken from the above study which looked at varying hypoxic exposures ranging from lifetime through to intermittent hypoxia at rest (ie repeated cycles of a few minutes of alternate hypoxia and normoxia). The findings indicate that subjects experiencing several weeks of continuous exposure to hypoxia, such as returning mountaineers, far from showing positive training benefits, actually had no increase in capilliarisation but had suffered a significant loss of muscle fibre cross sectional area. In addition, there was a loss of mitocondrial volume of close to 30% and a resultant significantly reduced VO2max. Similar reduced levels of mitocondrial volume density and capillary supply (compared to 'low landers') were found in lifetime 'high livers', and yet they are well known to excel at altitude. This apparent paradox of having superior aerobic performance in hypoxia and having modest muscle oxidative capacities has been found to result from adaptive physiological mechanisms, including an up-regulation of EPO.

Having explored life-time and long term exposure to hypoxia they then went on to explore whether hypoxia could induce performance benefits for 'low-landers')

Short-term hypoxia exposure

We reasoned that hypoxia might still be an important stimulus related to exercise in muscle tissue. However, the stimulus of hypoxia could be negated under chronic altitude conditions such that hypoxia may negatively interfere with recovery processes including signalling events, transcription, translation and protein synthesis. We thus decided to explore hypoxia protocols under which hypoxia was present only during the exercise session but not during recovery (e.g living low–training high). Four groups of initially untrained subjects were set up to train five times a week for a total of 6 weeks on a bicycle ergometer.

Two of these groups trained at 560 m (normoxia) and two at simulated 3850 m (hypoxia; $F_{I,}$J of 13 %). For each of the oxotensic groups, one trained at the anaerobic threshold (high intensity) and the other at about 25% below this level (low intensity). Analysis of pre- and post-training biopsies of m. vastus lateralis revealed that total mitochondria increased significantly in all groups; in contrast, subsarcolemmal mitochondria, i.e. those located near capillaries, increased significantly only in those groups training under hypoxic onditions, irrespective of training intensity. Noticeably, the group which trained at high intensity in hypoxia showed the highest increase in total mitochondrial volume density (+59 %) and capillary length density was increased significantly in this group only (+17.2 %) (Geiser *et al.* 2001; Vogt *et al.* 2001). These results indicate that strenuous training in hypoxia while living near sea-level leads to muscle adaptations which compensate the reduced availability of oxygen by improving the conditions for transportation and utilization of oxygen in exercising muscle. Several studies performed under the paradigm of 'living low–training high' indicate that performance or $VJ_{,max}$ in hypoxia is improved more after hypoxia than under normoxia training (Terrados *et al.* 1988, 1990; Desplanches *et al.* 1993; Bailey *et al.* 2000; Meeuwsen *et al.* 2001), while some others do not (Emonson *et al.* 1997; Melissa *et al.* 1997; Ventura *et al.* 2002). Despite these discrepancies reported for functional changes, it was shown that the activity of citrate synthase was increased more

after training under hypoxic conditions than after the same training under normoxic conditions (Terrados *et al.* 1988; Melissa *et al.* 1997; Green *et al.* 1999). These results support our finding of a hypoxia-induced increase of muscular oxidative capacity and mitochondrial density (Geiser *et al.* 2001). Furthermore, improvements of anaerobic performance were shown by Meeuwsen (Meeuwsen *et al.* 2001) when he trained eight cyclists at a simulated altitude of 2500 m and another group at sealevel, 2 h per day for 10 days. Beside significant increases in $\dot{V}O_{2,max}$ and maximal power output, a Wingate test showed increased anaerobic performance parameters only for the hypoxia training group. Analysis of mRNA expression in the muscle biopsies from the subjects of our hypoxia training study hint at the molecular changes possibly responsible for the functional adaptations in skeletal muscle to hypoxia. The mRNA of hypoxia-inducible factor 1a (HIF-1a), which drives transcription of hypoxia-inducible genes (Semenza, 1999), is increased after training under hypoxic conditions irrespective of training intensity, but not after training in normoxia (Vogt *et al.* 2001). Moreover, we found VEGF, myoglobin and phosphofructokinase mRNA increased with training at high intensity in hypoxia but not in normoxia. The expression of the latter two genes can be induced by HIF-1a following its stabilisation in hypoxia (see below; Semenza, 1999).

In conclusion, molecular and functional results reveal that a hypoxic stimulus, which is only present during an exercise session, can lead to additional muscular and systemic adaptations as compared to the same training regime in normoxia. For athletes, hypoxia training can be a way to improve performance for competition at altitude and eventually also at sea-level.