PERMANENT AND INTERMITTENT HYPOXIA AS RESPONSE MODIFIERS OF SKELETAL MUSCLE TISSUE WITH EXERCISE TRAINING

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RESUMEN: Hipoxia Permanente e Intermitente Como Modificadores de Tejido Muscular Esquelético En Ejercicio de Entrenamiento

Es una creencia todavía ampliamente sostenida que el músculo esquelético de animales y humanos expuestos a hipoxia crónica tiene una capacidad oxidativa y una capilaridad incrementadas. Sin embargo, el análisis de biopsias de humanos tanto antes como luego de ascensos reales o simulados a los Himalayas, ha demostrado consistentemente una disminución en la capacidad oxidativa y una capilaridad sin cambios. Más aun, en biopsias de vastus lateralis de indígenas de altura de Los Himalayas y Los Andes, el contenido mitocondrial estaba marcadamente reducido en comparación con el de nativos de nivel del mar emparejados por edad y estado de entrenamiento. En conjunto, estos estudios indican que la exposición permanente a hipoxia severa (producida por vivir a alturas por encima de 3500 m) producen una disminución en la capacidad oxidativa así como en el rendimiento aeróbico. Si se produce hipoxia severa solamente durante las sesiones de entrenamiento, entonces las mejoras resultantes son comparables a las producidas por entrenamiento por un período similar bajo condiciones normóxicas. Adicionalmente, se observa que el volumen del músculo esquelético y la concentración de mioglobina aumentan con el entrenamiento en hipoxia pero no en normoxia. Teniendo en cuenta estos hallazgos, los atletas deberían limitar su exposición hipóxica al período mínimo compatible con la inducción de una respuesta eritropoyética. Si se desea una ganancia en la masa muscular oxidativa y en la concentración de mioglobina, deberían lograrse por sesiones de entrenamiento bajo condiciones de hipoxia severa.. Los mecanismos celulares responsables de la respuesta del tejio muscular esquelético a la hipoxia no se conocen actualmente.

Palabras claves: Altitud, Humano, Ejercicio de entrenamiento, Estructura muscular, Capilar

Hypoxie permanente et intermittente en tant que modificateurs de la réponse du tissu musculaire squelettique aux exercices d'entraînement.

Selon une croyance encore très répandue, le tissu musculaire squelettique des animaux et des humains exposés à l'hypoxie chronique aurait une capacité oxydative renforcée et une capillarité accrue. L'analyse des biopsies faites sur des sujets après des ascensions réelles ou simulées dans les montagnes de l'Himalaya a démontré de manière constante une diminution de la capacité oxydative musculaire et une capillarité inchangée. En outre, des biopsies du *vastus lateralis* provenant de populations natives de l'Himalaya et des Andes ont révélé que le contenu mitochondrial était nettement diminué comparé à celui des natifs du niveau de la mer, appariés en fonction de l'âge et du degré d'entraînement. Ces études indiquent que dans l'ensemble l'exposition permanente à l'hypoxie sévère (due au fait de vivre à plus de 3500 m d'altitude) entraîne une diminution de la capacité oxydative musculaire ainsi que du rendement aérobique du travail. Si l'hypoxie sévère ne se produit qu'au cours de séances limitées d'exercices d'endurance, les améliorations obtenues sont comparables à celles résultant d'un entraînement de même durée dans des conditions normoxiques. On observe en outre une augmentation du volume du muscle squelettique et de la concentration de myoglobine avec l'entraînement en hypoxie, mais pas en normoxie. Compte tenu de ces découvertes, les athlètes d'endurance devraient limiter leur exposition à l'hypoxie à la durée minimum nécessaire à l'induction d'une réponse de l'érythropoïétine. La recherche d'un gain de la masse musculaire oxydative et de la concentration de myoglobine devrait se faire au cours de séances d'entraînement se déroulant dans des conditions hypoxiques sévères. Les mécanismes cellulaires responsables de la réponse du tissu musculaire squelettique à l'hypoxie ne sont pas connus actuellement.

Mots-clés : Altitude, Humain, Exercice, Entraînement, Structure, Muscle, Mitochondries, Capillarité, VO_{2max}, Hypoxie.

ABSTRACT It is still a widely held belief that the skeletal muscles of animals and humans exposed to chronic hypoxia have an enhanced oxidative capacity and increased capillarity. However, analysis of biopsies from subjects both prior to and after real or simulated ascents to the Himalayas have consistently shown a decrease in muscle oxidative capacity and an unchanged capillarity. Furthermore, in vastus lateralis biopsies derived from highland populations indigenous to the Himalayas and Andes, the mitochondrial content was markedly reduced in comparison with that of lowlanders matched for age and training status. Combined, these studies indicate that permanent exposure to severe hypoxia (incurred by living at altitudes above 3500m) elicits a decrease in muscle oxidative capacity as well as in the aerobic work performance. If severe hypoxia is incurred only during the constrained limits of endurance training sessions, then the resulting improvements are comparable to those elicited by training for a similar period under normoxic conditions. Additionally, it is observed that skeletal muscle volume and myoglobin concentration increase with training in hypoxia but not in normoxia. Bearing these findings in mind, endurance athletes should limit their hypoxia exposure to the minimum period commensurate with induction of an erythropoietin response. If a gain in oxidative muscle mass and myoglobin concentration are desired, then they could be achieved by training sessions conducted under severe hypoxic conditons. The cellular mechanisms responsible for the response of skeletal muscle tissue to hypoxia are currently not known.

Key words: High altitude, Human, Exercise training, Muscle, Structure, Mitochondria, Capillary, VO_2 max, Hypoxia

Background

Since the late fifties and early sixties, there has been seemingly incontrovertible experimental evidence that continuous exposure to a hypoxic environment, such as is incurred by living at high altitude, leads to characteristic modifications in skeletal muscle tissue. Valdivia (1958) demonstrated a significantly increased capillarization of skeletal muscles harvested from guinea pigs native to high altitudes as compared to those derived from sea-level controls. Reynafarje (1962) found higher myoglobin and cytochrome reductase concentrations in sartorius muscle biopsies obtained from subjects living permanently at 4400m above sea level (in the mining city of Cerro de Pasco) than in controls living at sea-level (Lima). These milestone findings had a profound influence on people's ideas concerning the effect of local hypoxia on muscle structure and function. And when, a decade later, it was demonstrated that continuous endurance exercise training leads to an increase in muscle oxidative capacity (Holloszy et al 1970; Hoppeler et al. 1973), as well as increasing its muscle capillarity (Andersen 1975), these changes were accordingly attributed to (a putative) local tissue hypoxia experienced during training sessions. In 1983, Hochachka condensed what was then the generally accepted view of the mechanisms responsible for high altitude acclimatization into what he called an "interpretative hypothesis". He proposed that an organism living at high altitude was faced with the problem of "maintaining an acceptably high scope for aerobic metabolism in the face of the reduced oxygen availability of the atmosphere". This was envisaged as being achieved (a) by increasing the capacity of oxygen transfer to the tissues and (b) by augmenting the capacity for oxidative metabolism at the periphery by an increase in mitochondrial enzyme activity. By these means, the increase in capillary density, decrease in diffusion distance, increased capacity for facilitated diffusion and enhanced oxidative capacity of muscles could all be explained within a coherent conceptual framework. This interpretation of the "classical" high-altitude results also suggested that exposure to hypoxia, such as that experienced in high-altitude training camps, was beneficial for the capacity of muscle tissue to transfer and utilize oxygen. However, an ever-increasing body of experimental evidence now throws serious doubt upon the tenability of Hochachka's hypothesis, at least as far as humans are concerned.

Lowlanders exposed to continuous severe hypoxia

During the late eighties and early nineties, a number of studies became available reporting results of skeletal muscle changes observed as a consequence of prolonged exposure to severe hypoxia at altitudes above 5000m for several weeks, as a consequence of experiments conducted during simulated (Green et al.1989) or real (Hoppeler et al.1990; Howald et al.1990) attempts to climb Mount Everest. The general consensus among these studies is that muscle tissue oxidative capacity is reduced (by about 20-30%), rather than increased after high-altitude exposure. Such a change is, moreover, accompanied by an approximately 10% decrease of muscle cross-sectional area and a concomitant reduction in fiber size of similar magnitude (see Hoppeler et al.1990). Consequently, subjects returning from an Everest expedition have a smaller muscle mass with a decreased oxidative capacity. This massive reduction in total peripheral oxidative capacity is believed to be partially responsible for the reduction in VO_2 max registered after high-altitude exposure (Hoppeler et al.1990). It could also be demonstrated that the increase in capillary density (i.e. the number of capillaries per mm^2 of muscle fiber) observed after high-altitude exposure is not a consequence of capillary neoformation but rather of the reduced muscle fiber size, the absolute extent of the capillary network remaining essentially unchanged. Nonetheless, the decrease in fiber size combined with the increased myoglobin concentration (Reynafarje 1962; Terrados et al.1990) will most likely improve the oxygen transfer conditions from erythrocytes to muscle mitochondria. Since high-altitude training camps are usually situated at a moderate altitude (between 1800 and 2500m), rather than at the extreme altitudes necessary for successful attempts of climbing the highest peaks, one would not expect the "negative" muscle changes incurred by athletes training at these altitudes to be as dramatic as those observed in "extreme" climbers; but that high-altitude training is "good" for your muscles can no longer be regarded as a valid tenet.

Permanent high-altitude residents

As Hochachka's "interpretative hypothesis" was based primarily on data obtained from highaltitude-adapted animals, such as llamas, we wished to further explore the effects of permanent high-altitude residency on human muscle structure. One set of studies was carried out on Tibetans, inhabitants of the Tibetan highland for many generations, (Kayser et al. 1991), and another on permanent high-altitude residents of multi-ethnic background in La Paz, Bolivia

(3600m). In both populations, muscle tissue oxidative capacity, measured by the volume density of mitochondria as well as by the activities of oxidative enzymes, was significantly lower (approximately 20%) than that in lowlanders matched for age, socioeconomic status and training background; both high-altitude populations also had a lower capillary-to-fiber ratio. Interestingly, Tibetans tended to have a reduced fiber size, which was not observed in Bolivians, and their capillary density was consequently higher. Recent data pertaining to lowland-born Tibetans (Kayser et al. 1996) strongly suggest that these structural modifications are inherited. Taken together, the data on high-altitude populations indicate that permanent, severe hypoxia leads to a significant reduction in the aerobic work capacity of muscle tissue. Athletes residing at these altitudes will thus be at a considerable disadvantage when competing under sea-level conditions. It is interesting to note that inhabitants of the Ethiopian highland (1800-2800m) appear to perform exceedingly well in long-term endurance events. This population has, to my knowledge, not been extensively studied, and it therefore remains open to speculation whether the Ethiopians can profit from the somewhat lower elevation of their natural environment or whether they have a better genetic predisposition. This apparent paradox certainly merits further investigation.

Training in severe normobaric hypoxia

In order to put Hochachka's "interpretative hypothesis" further to the test, we reasoned that whilst permanent hypoxia was obviously detrimental to anabolic events in muscle, acute exposure might in fact serve as an excellent stimulus for improving its aerobic work capacity. It is, indeed, widely recognized that a decrease in ambient oxygen partial pressure has a negative influence on cultured cell growth. We therefore devised an experimental protocol in which subjects were exposed to severe normobaric hypoxia (equivalent to an altitude above 4000m) by decreasing oxygen concentration in the inhaled air during training sessions. Our results indicate that when an endurance training regime of comparable intensity is carried out under normoxic and severe (intermittent) hypoxic conditions, similar, but not identical effects are elicited in skeletal muscle structure. Subjects trained in both environments had similar increases in capillary supply and mitochondrial volume density, but those exposed to hypoxia had additionally a 10% increase in muscle and fiber cross-sectional area. It may be worth mentioning here that such a response is not achieved by endurance training in previously untrained males (Hoppeler et al. 1985), and that the increase in muscle crosssectional area is more than half of that achieved after a similar number of strength-training sessions (Luthi et al. 1986). Since such a gain in muscle cross-sectional area after endurance training has a potential significance for athleticism, we have since repeated this study using a larger number of subjects, and the data thereby gleaned serve only to corroborate the findings delineated above (Geiser and Hoppeler, unpublished results).

Conclusions for athletic training

Data pertaining to the changes in muscle structure elicited by exposure to high-altitudes need to be considered in the light of other relevant performance-determining physiological variables notably modifications in the hormonal status. Additionally, one has to consider whether the competition, an athlete trains for, is held at high- or low-altitude. and finally, one has to keep track of "confounding variables", such as heat tolerance, high-altitude sleep disorders etc. when using altitude or hypoxia as an ergogenic aid.

Competition at high altitudes

Most exercise scientists would agree that it is usually a good strategy for athletes to train at the altitude at which the competition is to be held, acclimatization over a period of 3 weeks being sufficient. If for financial or logistic reasons, an adequate altitude-training for the necessary duration is not practicable, then it can be replaced by training sessions under hypoxic conditions. We used this method to advantage in preparing the Swiss Mountainbike team for the World Championships at Vail in 1994. Competitors were asked to undergo three strenuous training sessions per week under hypoxic conditions (30min, approx. 80% of VO_2 max) during the 3 week period prior to the race, with their race bikes mounted on rollers. This afforded participants with the opportunity of becoming used to working hard under hypoxic (race-) conditions. Although this experiment was not supervised closely from a scientific point of view, we nonetheless gained the impression that the reported benefit considered in the light of the excellent results achieved, was attributable to an enhanced facility for adjusting respiratory and leg muscle work to hypoxic conditions.

Competition at sea level

It is still a matter of dispute whether high-altitude training is of benefit for a competition taking place at sea level. Recent data by Levine and Stray-Gundersen (manuscript) suggest that the best strategy for an athlete relying heavily on his aerobic work capacity during competition (i.e.

activity exceeding a 2 minutes duration) is to live at moderate altitude (approximately 2000m) and train at low altitudes. The sojourn at moderate altitude permits an augmentation of VO_2 max by increasing the mass of circulating erythrocytes; the training at low altitude enables the athlete to sustain high levels of training intensity, which is of technical advantage and results in an increased VO_2 at the maximal possible steady state.
As an alternative to living at high altitude, athletes can, of course, also sleep in a house with a reduced oxygen atmosphere at sea level (a so-called "Finnish House"). All these training paradigms must necessarily take into account the potentially negative effects related to highaltitude sojourn, such as sleep disorders or different temperature and humidity conditions (discussed by Roach in this issue). One might additionally consider the use of severe hypoxia during training sessions as a means of increasing the physiological effects of the exercise stimulus; this should allow a gain in muscle mass durÍng aerobic training. The potential benefits of utilizing hypoxia in this way during preparatory off-season training would appear to be patent. And yet, few teams, if any, employ hypoxia as an ergogenic aid. In the context of its assets, it would be interesting to ascertain whether acute hypoxia applied during strength-training sessions would induce an augmented skeletal muscle response to high intensity loads.

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