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The effect of maternal exercise and altitude training on performance in hypoxic environment: a brief review

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Abstract

Environmental and maternal exercise experienced even during the very earliest stages of life has the potential to cause developmental changes. The growing evidence demonstrated that diverse environmental stressors affect offspring in various aspects in early stage of life and can be transmitted directly or indirectly by both parental lines. The development of normobaric hypoxic environment facilities began in recent years after athletes born and trained at high altitude continued to update their records in sports competition, especially marathons and other endurance sports. Although a large number of studies have proved the effect of hypoxic training in the field of sports science and competition, the effectiveness of this training model on exercise performance/capacity and physiological variables is still controversial. Therefore, this study makes a brief review of the papers related to this scope and attempted to understand the potential mechanism of maternal exercise in hypoxic environment on exercise performance and reduction of metabolic risk factors.

Key words: hypoxia, hypoxic environment, maternal exercise, exercise performance, metabolic syndromes

Introduction

The development of normobaric hypoxic environment facilities began in recent years after athletes born and trained at high altitude continued to update their records in sports competition, especially marathons and other endurance sports. The influence of hypoxic environment on competitive ability has aroused great interest. In preparation for the Mexico Olympics in 1968 that was to be held at an altitude of 2,400 m above sea level, countries with advanced sports performance began to explore methods to adapt to and train in various hypoxic environments. Most of the studies on the human body exposed in high altitude nature environments are carried out by mountaineering experts or athletes to adapt to high altitude training(Loshbaugh, Loeppky, & Greene, 2006; Schena, Guerrini, Tregnaghi, & Kayser, 1992). However, even after 50 years of extensive research on energy metabolism after temporary high-altitude training in athletes born, raised, and trained at sea level, the reasons behind the failure to parallel the athletic performance of athletes born, raised, and trained at a high altitude

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remain elusive. In addition, due to exposure to high altitude will cause acute mountain sickness(AMS), cold, decreased physical function and other stress reactions, the application of high altitude nature environment has some limitations, it is difficult to be widely used in ordinary people(Benso et al., 2007; Florian, Jankowski, & Gutkowska, 2010).

People who live at sea level are also known to lose weight when they are exposed to high altitudes, that is, a hypoxic environment(Armellini et al., 1997; Benso et al., 2007; Fusch et al., 1996; Major & Doucet, 2004). Further, cellular hypoxia induced by exposure to hypoxic environment occasionally occurs in people who emigrated to a high-altitude region. It not only shows the major pathological and physiological characteristics of diseases such as heart failure and chronic obstructive pulmonary disease but also may cause an imbalance of protein synthesis/degradation in skeletal muscles, energy metabolic impairment, and muscle cell apoptosis, ultimately leading to skeletal muscle atrophy and weakening of muscle capacity(Murray, 2009).

However, exercise training under hypoxia conditions is known to have several benefits, including increased in blood levels of red blood cell(RBC), hemoglobin(Hb), and hematocrit (Hct)(Chapman, Stray-Gundersen, & Levine, 1998), increased in the density of vascular endothelial growth factor (VEGF) (Harris, 2002; Semenza, 1998), myoglobin(Hahn & Gore, 2001), mitochondria and capillaries density in muscle(Desplanches et al., 2014; Desplanches et al., 1993; Hoppeler, Klossner, & Vogt, 2008; Lundby, Calbet, & Robach, 2009), and the transport and utilization of oxygen in skeletal muscle, improvement angiogenesis and muscle capillarization(Vogt & Hoppeler, 2010); as well as in the biosynthesis and phosphorylation of mitochondria in skeletal muscle(Bo, Zhang, & Ji, 2010).

From this perspective, sports science researchers have begun to explore various adaptation and training methods in hypoxic environments to enhance performance at higher altitudes in preparation of the Mexico Olympics in 1968, which was to be held at 2,400 m above sea level. These strategies include intermittent hypoxic training (IHT), living high - training low (LHTL), living low - training high (LLTH), living high - training high (LHTH), and living high - exercise high - training low (LHEHTL). However, which of these training methods is the most effective method to optimize aerobic exercise capacity for athletes remains controversial(Desplanches et al., 1993; Levine, 2002; Levine & Stray-Gundersen, 1997, 2001).

The failure to reach a consistent conclusion among studies is mainly attributable to the differences in participant selection, altitude for training, intensity and duration of training at high altitude, and selected measurement variables. However, most of all, this is a result of assessing the outcomes of high-altitude training after living at a high altitude only temporarily or simply comparing with athletes who were born and trained at a high altitude.

Maternal exercise and Hypoxic environment

Both genetic and environmental factors influence human growth and development. Environmental factors are involved in development in early life, and they have growth and developmental potential beyond the limitations of genetic traits(Aiken & Ozanne, 2014; Gilbert, 2001; Patti, 2013; Susser et al., 2012). Studies have reported that the genetic characteristics of conspecifics and effects of the range of viable environment, that is, exercise, nutrition, or environmental regulation during the conception process are intimately associated with growth and health of the subsequent generation(Moore et al., 2004).

Previous studies from the perspective of nutrition have pointed out that excessive calorie intake before pregnancy may lead to obesity and muscle weakness in offspring(Bayol, Macharia, Farrington, Simbi, & Stickland, 2009; Bayol, Simbi, Bertrand, & Stickland, 2008; Ng et al., 2010), while limiting maternal protein

intake may lead to low birth weight and metabolic dysfunction in adulthood(Ng et al., 2010; Peixoto-Silva, Frantz, Mandarim-de-Lacerda, & Pinheiro-Mulder, 2011).

Although several studies have been conducted, the impact of maternal exercise on offspring after birth is yet to be elucidated, except for some studies finding that exercise during pregnancy has significant impacts on the mother and fetus. Some recent studies confirmed that prenatal and postnatal endurance exercise has a positive impact on child's body composition and glucose and insulin metabolism (Carter et al., 2012; Carter, Qi, De Cabo, & Pearson, 2013; Pinto & Shetty, 1995). On the other hand, however, one study reported that maternal exercise training lowers neonatal body weight by reducing percent body fat(Clapp & Capeless, 1990; Kalisiak & Spitznagle, 2009).

In a sense, hypoxic environment is a physiological challenge and an environmental stress condition that induces organisms' adaptation, and natives of highlands have genes adjusted to the hypoxic environment(Michiels, 2004). In highlands, organisms undergo a homeostatic reaction to the shortage of oxygen, which helps them adjust to the high-altitude environment, and such adaptation may influence subsequent generations as a genetic factor(Ge et al., 1994).

Moreover, the theory of evolution explains pregnancy as an important stage that establishes the genetic traits of the fetus, and abnormal fetal growth in the uterus may increase the risk of cardiovascular diseases(Moret, Covarrubias, & Coudert, 1971). Based on these phenomena, hypoxic environment has been a major topic of research in the studies of ecology and evolution(MacInnis & Rupert, 2011; Mousseau & Fox, 1998; Uller, 2008), and the impact of maternal or paternal exercise training on subsequent generations has attracted much research interest in the field of sports medicine. Interestingly, physical performance declines with increasing altitude, but natives who have lived in highlands over several generations have been confirmed to have superior physical performance to that of people who emigrated to highlands(Sun et al., 1990; Weitz, Liu, He, Chin, & Garruto, 2013).

Such physical superiority of natives of highlands may be an ethnic feature, but it may also be a result of secondary adaptation to hypoxic environment. It is a fact that residents of highlands often have an elevated red blood cell count, such as polycythemia, to deliver oxygen and high myoglobin, mitochondria, and capillary density in muscles, thereby having an enhanced ability to transport oxygen to tissues and utilize oxygen in tissues.

Considering the reality in which athletes from some African countries who were born, raised, and trained in highlands at 2,000-3,000 m above sea level lead and set world records in middle and long distance running, concurrently examining the effects of multi-generational growth and exercise training in hypoxic environment would be highly significant. In particular, considering that middle-and long-distance athletes who grow up and trained at sea level cannot compare with their peers born in a hypoxic environment in terms of sports performance, even for implemented short term exercise training at high altitude(4-16 weeks). A long-term study design over several generations is essential to assess the characteristics of athletes born accurately and assess the effects of training at high-altitude for sea level athletes.

In a recent study on 1,250 natives of highlands(Yang et al., 2016), reported that these natives have a modified HMOX2 gene. This gene suppresses the excessive elevation of red blood cells, that is, polycythemia, which may be induced by prolonged habitation in highlands, thereby maintaining red blood cell and hemoglobin levels in normal ranges. This gene enables natives of highlands to maintain an appropriate blood red blood cell and hemoglobin levels while living and during exercise training at a high altitude, rendering their training more effective compared to that of people who live at sea level. However, it is yet unclear whether this is a result of the low oxygen concentration itself or is influenced by activities in a hypoxic environment.

Maternal exercise and Mitochondria

Mitochondria, well known as the cell's "energy plant" and "energy conversion center," is one of the most critical organelles in cells(Lehman et al., 2000), and mitochondria in skeletal muscles have been reported to be more heavily influenced by maternal DNA(Newgard, Hwang, & Fletterick, 1989). In a cell, mitochondria take charge of the cell's physiological functions through continuous synthesis and degradation under the regulation of nuclear genes and mitochondrial genes. Mitochondrial biogenesis refers to proliferation of mitochondria during a cell cycle and mitochondrial system synthesis(Meisinger, Sickmann, & Pfanner, 2008; Taylor et al., 2003). In light of reports that elevated expression of the PGC-1α protein in skeletal muscles and myocardial cells induces mitochondrial biogenesis, PGC-1α is considered a classic parameter for mitochondrial biogenesis(Levett et al., 2012; Little, Safdar, Bishop, Tarnopolsky, & Gibala, 2011; Pilegaard, Saltin, & Neufer, 2003). Elevated expression of the PGC-1α protein in skeletal muscles is accompanied by elevated expression of the NRF-1, mtTFA, and COX-IV proteins, and such elevation has been observed to increase the number of mitochondria and biogenesis capacity(Carraway et al., 2010; Z. Wu et al., 1999).

Muscle contraction activities as a result of exercise or other external stimuli may enhance the levels of mRNA and proteins for many transcription factors and particularly, may induce mitochondrial biosynthesis(Hood et al., 2003; Irrcher, Adhihetty, Joseph, Ljubicic, & Hood, 2003). PGC-1α (peroxisome proliferator-activated receptorγ coactivator-1α) is the classic parameter of mitochondrial biogenesis, and PGC-1α induces mitochondrial biogenesis by stimulating the nuclear respiratory factor-1,-2 (NRF-1,-2) and mitochondrial transcription factor A (mtTFA)(Johnson, Robinson, & Nair, 2013)). Further, COX-IV is an indicator of oxidative phosphorylation in mitochondria and aerobic exercise capacity and is regulated by NRF(Geng et al., 2010). Muscle contraction caused by one-time exercise or exercise training is known to enhance mitochondrial biogenesis and functions via expression of proteins such as PGC-1α and COX-IV(Demory et al., 2009; Jiandie Lin, Handschin, & Spiegelman, 2005; J. Lin et al., 2002; Miura et al., 2006; Terada & Tabata, 2004). In addition, training in hypoxic environment has been reported to increase expression of some proteins(Chitra & Boopathy, 2014; Desplanches et al., 1993; Geiser et al., 2001; Melissa, MacDougall, Tarnopolsky, Cipriano, & Green, 1997; Terrados, Jansson, Sylven, & Kaijser, 1990; Vogt et al., 2001).

Exercise is known to play an important role in enhancing the mitochondrial functions in skeletal muscles(Irrcher et al., 2003; Lanza & Nair, 2009; Short, Nair, & Stump, 2004), and improvement of mitochondrial volume and functions from exercise training has been considered an important means to boost performance of endurance athletes(Hawley & Lessard, 2008; Holloway et al., 2009).

However, not many studies have examined the effects of maternal exercise before and during pregnancy in improving mitochondrial biogenesis and functions, and particularly, studies that investigate the aerobic capacity of organisms born and raised in a hypoxic environment and the effects of multi-generational maternal endurance exercise on subsequent generations are completely lacking.

The Metabolic Characteristics of Highlanders

Commonly, the growth and hight of animals or plants at high altitude regions is slower or smaller compared to sea level. The hypoxic environment also affects the energy balance and growth of animals, including humans, and the altitude that affects human function is considered at the level of 5000-5500 meters above sea level(Kayser & Verges, 2013). Recently, it has been reported that the body composition and metabolic

characteristics of highlanders have lower prevalence and metabolic risk factors of metabolic diseases than people living at sea level.

Among the Aymara tribe in Chile, where BMI is similar to those living at sea level in South America (BMI>30), but the prevalence of diabetes is said to be relatively low(Santos, Perez-Bravo, Carrasco, Calvillan, & Albala, 2001). The BMI of Tibetans living at different high altitude(1200m, 2900m and 3600 m) in Nepal and Tibet was investigated, and the effect of obesity rates was analyzed. The results showed altitude itself affects energy intake and physical activity(Sherpa et al., 2010). In other words, the hypoxic environment itself may reduce the intake of energy sources and increase energy consumption. Furthermore, Wu et al. (2007) workers (obese) involved in railway construction between Qinghai and Tibet (3000-5000 meters above sea level) returned to normal weight during 3-5 months of operation(T. Y. Wu et al., 2007). Schobersberger et al. (2003) also studied patients with metabolic diseases and found that blood pressure and metabolic risk factors decreased after staying at 1700 meters above sea level for three weeks(Schobersberger et al., 2003).

Hypoxic and metabolic syndromes

Obesity is no longer the time to imagine that Westerners are exclusive. Obesity has also been a social problem in Asian countries since 2000. When it comes to health, the proportion of being overweight or obese is higher than ever. As obesity increases the risk of metabolic diseases such as insulin resistance, hypertension, diabetes, cancer, cardiovascular disease and Obstructive sleep apnea(OSA), it begins to become a social concern and an economic burden on the country. OSA, which often occurs in obese people, not only increases the risk of cardiovascular diseases but also increases the risk of metabolic diseases. Intermittent apnea leads to a decrease in oxygen supply and aggravates the chronic inflammatory response of fat cells.

Nevertheless, recently, a critical study found that exposure to intermittent hypoxia reduces metabolic risk factors in obese patients. In other words, exposure to intermittent hypoxia can lose weight and therefore reduce metabolic risk factors. In fact, in the former Soviet Union, the hypoxia environment is very effective in relieving high blood pressure. Hypoxic environmental exposure has been reported as an effective intervention for weight loss. It is understood that according to this theoretical basis, a hypoxia exposure such as high altitude will increase the appetite-suppressing hormone Leptin(Loshbaugh et al., 2006), increase basal metabolic rate(BRM), and promote a decline in body fat(Pearce, Williams, Hamade, Chang, & White, 2006).

It is reported that hypoxic environment exposure can increase tissue oxygen supply, capillary density(Lecoultre et al., 2010), regulate the synthesis rate of mitochondria in skeletal muscle(Zoll et al., 2006), and promote the secretion of hormones related to energy metabolism, thus activating fat metabolism(Barnholt et al., 2006). At present, the mechanism of increased energy consumption during hypoxia exposure has not been fully identified, but it is believed that one of the main reasons is the activation of sympathetic nervous system(Louis & Punjabi, 2009; Mawson et al., 2000).

Exercise in hypoxic environment can promote mitochondrial biosynthesis, increase the process of fatty acid oxidation in muscle(Gilde & Van Bilsen, 2003; Zoll et al., 2006), increase the density of capillaries, the number and efficiency of muscle oxidase and mitochondria, thus activate fat metabolism(Lecoultre et al., 2010; Roels et al., 2007).

On the other hand, the increase of autonomic nervous activity under hypoxia environment, as an energy source, also proposes another possibility to promote the utilization of glucose and glycogen(Azevedo, Carey, Pories, Morris, & Dohm, 1995; Kelly et al., 2010). Hypoxia environment will increase the level of glutamate carrier protein GLUT-4, which not only promotes glucose metabolism but also may increase

insulin sensitivity(Chiu et al., 2004; Chou et al., 2004; Mackenzie, Maxwell, Castle, Brickley, & Watt, 2011). Another main reason for the decrease of body fat during intermittent hypoxia exposure is that the hypoxia environment activates the mechanism of inhibition of appetite center, increases the capacity of oxygen transport, and improves the transport and decomposition of fat energy sources; thus the possibility of activating sugar and fat metabolism was proposed(Camacho-Cardenosa et al., 2018; Wenger, 2002).

In addition, physical exercise in a hypoxic environment can achieve the effect of high-intensity exercise at sea level, even with lower intensity training at sea level(Camacho-Cardenosa et al., 2018). It may be the most suitable non-drug intervention for highly obese people, patients with skeletal muscle systems and the elderly who can only do low-intensity exercise.

Potential mechanism underlying reducing metabolic risk factors

The possibility that the hypoxia environment itself reduces the metabolic risk factors, that is, the possibility of weight loss in the hypoxia environment is largely due to loss of appetite and increased energy consumption, both of which can be predicted. Changes in hormones related to the appetite center do reduce appetite at an altitude of more than 5000 meters, but weight loss does not occur if they lose weight according to the subjects' appetite and eating habits. In particular, it is almost impossible to count on the weight loss effects of appetite inhibition when intermittently exposed to hypoxia at sea level. The regulation of energy intake and consumption is maintained by energy balance sensing mechanism. Therefore, a signal protein (AMP-activated protein kinase, AMPK) is considered to play an important role in the regulation of energy intake and consumption, which acts on the balance of energy intake and consumption. AMPK will respond to the increase or decrease in the production and consumption of ATP, especially when the ATP/ADP ratio decreases. The change in the proportion of ATP/ADP can be adjusted in a reduced energy source or in a hypoxic environment. The general role of AMPK in the body is to participate in the decomposition of energy, rather than the synthesis or storage of metabolites. Another mechanism for activating AMPK includes IL-6-AMPK, hypoxia, which increases muscle IL-6 and increases IL-6 activation of AMPK. Several researchers have studied the hypoxic environment increases IL-6 not only in healthy people but also in patients with hypoxia(Mazzeo et al., 2001; Klausen et al., 1997). Lundby & Steensberg(2004) analyzed the effects of grade and chronic hypoxia environment on IL-6 increased by exercise and reported the synergistic effect of exercise and hypoxia environment. Under the relative intensity, the concentration of IL-6 was no different from that in hypoxia and normal oxygen environment, but the concentration of IL-6 was higher in hypoxia environment at the same absolute maximum downward exercise. AMPK activity is regulated by Adipokine, such as energy source, sugar, leptin and adiponectin. Muscle leptin and lipoprotein activate AMPK to increase fat metabolism. In particular, adiponectin in the liver can increase fat metabolism and inhibit sugar production.

Picon-Reategui et al. (1970) believe that the fasting blood glucose content, erythrocyte and plasma sugar content of the population at high altitude are lower than those in the plain. The experimental results on glucose tolerance of people at high altitude are also very inconsistent. Sawhney et al. (1986) reported that glucose tolerance decreased at 3500m and increased after glucose load. In the plateau for 14 days, both the plain population and the native plateau population were significantly higher than those in the plain control group, and the native population was the highest. The content of plasma insulin in the immigrant population was significantly higher than that in the native population, and both of them were higher than those in the plain population. That may be due to the simultaneous increase of anti-insulin hormones caused by hypoxia at high altitude, which interferes with an

adaptive change in the effect of insulin on glucose metabolism. However, the medical research team of Mount Qomolangma in the United States, at an altitude of 6300m, found that the blood sugar content of the members was quite stable and did not increase after glucose load. When the plasma insulin increased after glucose load, the serum glucose content was lower than the plain value.

The inconsistency of these results is likely to be related to many factors such as residence time at altitude, dietary composition (especially sugars) and whether the heat energy is balanced or not. The ability of people at high altitude to use glucose is greater than that of people in plain. In the plateau environment, the utilization rate of glucose is increased, and there is a glucose threshold in the surrounding tissue, which is necessary for glucose to enter the tissue from the blood for metabolism. The low width value of the population at high altitude may be one of the reasons for the enhancement of the utilization ability of sugar in the population at high altitude, and it is one of the manifestations of their adaptability to hypoxia. In animal experiments, Lui et al. (2015) found that high-altitude exercise training (~4,300 m) for 6–8 weeks significantly improved maximum oxygen consumption (VO2max) in rat pups in low and high altitudes and that the degree of improvement was greater in rat pups in a high altitude than those in a low altitude. In contrast, there were no significant changes in rat pups that underwent exercise training at sea level. Recently, multiple studies have investigated the effects of such environmental and genetic characteristics on exercise capacity, such as VO2max and glycometabolism(Dabelea, Knowler, & Pettitt, 2000) or metabolic ability(Boney, Verma, Tucker, & Vohr, 2005; Catalano et al., 2009).

Conclusions

Many studies have attempted to identify the reasons why athletes born, raised, and trained at sea level cannot outperform athletes born, raised, and trained at high altitudes even with temporary elevation or enhancement of physical metabolism-related parameters induced by temporary high-altitude training. The failure to draw a consistent conclusion, however, may be mainly attributable to the differences in participant selection, altitude for training, intensity and duration of training at high altitude, and selected measurement variables. However, most of all, this is a result of assessing the outcomes of high-altitude training after living at a high altitude only temporarily. Nevertheless, studies examining people who have been born, growth, and trained at a high altitude over several generations are lacking.

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