Chinese Journal of Physiology 56(×): ×××-×××, 2013
DOI: 10.4077/CJP.2013.BAB130

Review

Altitude Training Improves Glycemic Control

Shu-Man Chen[1], Hsueh-Yi Lin[2], and Chia-Hua Kuo[3]

[1]*Committee for General Education, Shih Hsin University, Taipei*
[2]*Physical Education Office, National I-Lan University, I-Lan*
and
[3]*Laboratory of Exercise Biochemistry, Taipei Physical Education College*
Taipei, Taiwan, Republic of China

Abstract

Under altitude hypoxia condition, energy reliance on anaerobic glycolysis increases to compensate the shortfall caused by reduced fatty acid oxidation. Short-term moderate altitude exposure plus endurance physical activity has been found to improve glucose tolerance (not fasting glucose) in humans, which is associated with the improvement in the whole-body insulin sensitivity. However, most of people cannot accommodate high altitude exposure above 4500 M due to acute mountain sickness (AMS) and insulin resistance. There is a wide variation among individuals in response to the altitude challenge. In particular, the improvement in glucose tolerance and insulin sensitivity by prolonged altitude hiking activity was not apparent in those individuals with low baseline DHEA-S concentration. In rats, exercise training recovery under prolonged hypoxia exposure (14-15% oxygen, 8 h per day for 6 weeks) can also improve insulin sensitivity, secondary to an effective suppression of adiposity. After prolonged hypoxia training, obese abnormality in upregulated baseline levels of AMPK and AS160 phosphorylation in skeletal muscle can be reversed. In humans, moderate hypoxia increases postprandial blood distribution towards skeletal muscle during a training recovery. This physiological response plays a role in the redistribution of fuel storage among important energy storage sites and may explain its potent effect on the favorable change in body composition. Conclusion: Altitude training can exert strong impact on our metabolic system, and has the potential to be designed as a non-pharmacological or recreational intervention regimen for correcting metabolic syndromes.

Key Words: glucose tolerance, hypoxia, insulin sensitivity, metabolic syndromes

Introduction

To maintain living, cellular ATP is continuously consumed and must be regenerated in an equal pace. The regeneration of ATP, for the most part, is driven by energy released from oxidation of the reducing compounds-fatty acid and glucose. Oxygen serves as the final electron acceptor, receiving electrons that ultimately come from both energy-rich reducing compounds. Without oxygen presence, ATP regeneration will be compensated mostly by increasing the rate of anaerobic glycolysis (conversion of glucose to lactate). Therefore, reducing oxygen availability would undoubtedly impact our metabolic system by increasing energy dependence on glucose utilization. This has been nicely demonstrated by Ogita's laboratory that altitude exposure significantly elevates respiratory exchange ratio (RER) and increases lactate accumulation, in parallel with reduced glycerol release (from triglyceride breakdown) from periphery (17). In this paper, we will summarize our past findings and the current knowledge in the metabolic influence of altitude hypoxia training on carbohydrate metabolism.

Studies on Healthy Men

Insulin resistance, characterized by impaired carbohydrate metabolism, has now been found as the early sign of type 2 diabetes, coronary heart disease,

Corresponding author: Chia-Hua Kuo, Ph.D., Laboratory of Exercise Biochemistry, Taipei Physical Education College, 101 Jhongcheng Rd., Sec. 2, Shilin District, Taipei, Taiwan, R.O.C. Tel: +886-2-28718288 ext. 5802, Fax: +886-2-28753383, E-mail: kuochiahua@gmail.com
Received: June 5, 2012; Revised (Final Version): August 11, 2012; Accepted: August 21, 2012.
 ISSN : 0304-4920. http://www.cps.org.tw

hypertension, stroke, and cancer (12, 26). Above clinical events developed in approximately one out of three normal middle-aged adults who were in the upper tertile of insulin resistance at baseline, followed for an average of 6 years. Interestingly, it has been reported that both cardiovascular and cancer mortality rates in humans resided at moderate altitude are lower than those living at sea-level (2, 25). Knowledge regarding whether the recreational intervention of altitude can help to improve insulin sensitivity would be valuable, as aforementioned clinical event accounts for the majority of death in the modern aging society (1).

Altitude is characterized by hypoxia, low temperature, and low atmospheric pressure. Many researchers focused on hypoxia aspect of physiological response, since this component exerts potent effect on human metabolism. Our past experiment on hypoxia shows that oxygen concentration at 12% can be tolerable for the most of animals but still caused ~6% death rate. Thus, such risk should be prevented by lowering altitude hypoxia strength when it is utilized for clinical use. Based on this preliminary result, all of our experiments were performed using 14% oxygen or greater concentration.

High altitude to a level above 4500 M can create discomfort and thus unsuitable for humans to improve their insulin sensitivity. Larsen *et al.* reported that AMS and insulin resistance can be resulted in healthy young men (aged ~ 27 years old) after a quick passive ascent to a high altitude of 4559 m (~12% oxygen) (21). AMS is characterized by the symptoms of a headache plus at least one of the following symptoms: GI upset (loss of appetite, nausea, vomiting), fatigue/weakness, dizziness/light-headedness, insomnia. Under this condition, insulin-stimulated glucose uptake decreases by ~50%. The decreases in insulin action were associated with the increases in counter-regulatory hormones, such as cortisol and norepinephrine. Despite this acute insulin resistance state would not last long (less than a week), altitude at this level would be unpleasant to be used for clinical application.

Based on this fact, we designed a study to determine the effect of moderate altitude (3 days at 2400 M, ~16% oxygen) on glucose tolerance (22). Eight subjects (aged from 18 to 43 years) well-tolerated with only one participant had 1-day AMS. No vigorous physical training was performed during the study. Glucose tolerance but not fasting glucose levels was significantly improved after the 3 days of altitude exposure. We further tested the combined effect of altitude plus hiking activity on the same metabolic parameters in Pamirs confined to a highland area with altitude varying between 2500 and 4000 M (13-16% oxygen). The backpack load was controlled within 0.3 to 0.33 kg per kg body weight. Glucose concentrations during OGTT were measured at baseline and 3 days after the high-altitude hiking activities at ~4000 M. Glucose tolerance was significantly improved yet fasting glucose concentration was slightly elevated from ~85 to 102 mg/dl. Both experiments provide consistent evidence that short-term moderate altitude with or without increased physical activity can improve glucose tolerance in healthy humans.

Studies on Humans with Metabolic Syndromes

An Austria group investigated effects of recreational activity at altitude on 22 males with metabolic syndromes (27). During a 3-week stay at 1,700 m (~17% oxygen) in an Austrian mountain, HOMA-IR value (Homeostasis Model Assessment of Insulin Resistance) and glucose tolerance were significantly improved. Altitude at this level appears to be well-accommodated in these metabolically abnormal individuals.

Obesity is known as the major cause to accelerate age-onset insulin resistance and metabolic disorders in adults. We previously investigated the effect of 4-week altitude hiking on obese human subjects. The subjects were the individuals with a history of drug abuse (users of heroin, cocaine, or amphetamine). A huge regain in body weight (18-100% above their original body weight) was noted during abstention period. All subjects exhibited severe hyperinsulinemia (a sign of insulin resistance) following an oral glucose load. In this study, 9 male obese (age 28.7 ± 1.3 yr) and 17 control subjects (age 29 ± 1.1 yr) voluntarily participated in a 4-week hiking activity (altitude 2200-3800 M, 13-16% oxygen). After the altitude expedition, insulin levels during the OGTT in ex-addicts were completely normalized to control level. Along with the improvements, a significant reduction in waist-to-hip ratio, with a small increase in lean body mass was observed. Both studies confirm the health benefit of altitude activity for metabolically abnormal individuals.

Hypoxia Increases Basal Glucose Uptake in Heart

It has been reported that hypoxia increases glucose uptake in skeletal muscle (7). However, we need to aware that most of such experiments were performed under ischemic or anoxic condition (oxygen concentration close to zero), which is apparently lethal to humans and cannot comparable to high altitude hypoxia condition. Altitude hypoxia places human heart into a stressful condition since greater cardiac muscle contraction is needed to compensate reduced peripheral arterial oxygen. Using positron emission tomography (PET) with 2-deoxy-2-[^{18}F]

fluoro-D-glucose ([^{18}F]FDG) injection, we found that heart has higher priority for glucose supply from circulation than skeletal muscle under altitude hypoxia. An increased cardiac glucose uptake (by ~70%) in a simulated altitude hypoxia condition (14-15% oxygen) was observed, whereas no significant change in overall skeletal muscle glucose uptake (fasting sedentary condition). Despite heart contributes to small part of the whole body glucose uptake under fasted condition, it is worthy to acknowledge that moderate altitude hypoxia exert strong impact to this vital organ.

DHEA-S Underlies Individual Variation

Individual responses in glucose tolerance and erythropoiesis against altitude challenge vary widely among healthy humans (23). We firstly found that the serum dehydroepiandrosterone sulfate (DHEA-S) level dropped significantly at altitude in the subjects with higher baseline DHEA-S level, whereas those subjects with a lower baseline DHEA-S level remain stably low. To further elucidate the role of DHEA-S in the adaptation on glucose metabolism against altitude activity, subjects were then divided into lower and upper halves according to their baseline DHEA-S concentrations at sea-level. We found that glucose and insulin concentrations on an oral glucose tolerance test were significantly decreased by the mountaineering activity confined only to those subjects with initially higher DHEA-S. Similarly, increased hematocrit and hemoglobin concentrations in altitude were occurred only in the high DHEA-S group. Intriguingly, the low DHEA-S subjects exhibited a higher erythropoietin (EPO) value at both sea level and altitude than the high DHEA-S group, suggesting a resistance of hematopoietic system to EPO stimulation for erythropoiesis.

DHEA and its sulfate derivative DHEA-S, collectively, are the most abundant steroid in humans, which is mainly produced in the adrenal gland (3, 32). It is also the primary precursors in biosynthesis of many steroid hormones, known as androgens, estrogens, and some other steroid hormones. This endogenous steroid is generally known to decline with advancing aging. Baseline plasma DHEA-S concentration has been found to closely associate with human longevity and fitness.

Coping against acute stress generally involves with sudden increased oxygen demand, which can result in transient tissue hypoxia. Successful coping against variably environmental changes, such as muscular work, temperature shift, and mental challenge, is essential to ensure continuation of our well-being and survival. We previously found a prolonged decrease in circulating DHEA-S for 5 days in the golfers who received negative competition outcome, whereas the overall mood state (measured by Profile of Mood States (POMS) inventory) remained stable. The depression level on the losing golfers recovered quickly demonstrating that the psychological readjustment was successful with concurrent decline in the DHEA-S level. In contrast, the mood state and DHEA-S were not changed for the made the cut group throughout the entire observation period.

Coping with heat stress is one of the most important survival mechanisms for human body, since increasing body temperature can cause irreversible change in protein conformation and eventually leading to death. A state of insulin resistance, evidenced by increased area under curve of glucose and HOMA-IR values (insulin resistance indicator), was manifested in 16 healthy males with a 30-min hot spring immersion at 41°C. A wide range of individual variation for the heat-induced stress response was also identified. We found that changes in insulin resistance measures after heat stress is associated with baseline DHEA-S level. In particular, hot spring immersion-induced insulin resistance state was restricted only to the low DHEA-S group.

Hiking at altitude faces hypoxia and increased demand of oxygen during muscular work. We found a persistent reduction in DHEA-S level concurrent with improvement in insulin sensitivity during the recovery period after resistance exercise (30). Resistance exercise is known to generate considerable muscle damage and thereafter induces a protracted repair process. DHEA-S decline phenomenon appears to be related to increased consumption for tissue repair during recovery in damaged skeletal muscle. The increased demand on DHEA-S could account for consumption of this steroid during recovery, based on the evidence that exogenous DHEA administration following various conditions causing tissue damage enhances functional recovery (15).

Exercise training is generally recommended for elderly to maintain metabolic health. However, it was also reported that the training effect on improving glycemic control for middle-aged or older individuals is not as effective as for young individuals (28). We investigated the effect of a 4-month exercise training program on glucose tolerance and insulin sensitivity in a group of elderly, aged greater than 80 years, in relation to their baseline DHEA-S levels. The result shows that the 4-month exercise training effect on improving insulin sensitivity cannot occur in the elderly with low DHEA-S level (16).

Mechanism Associated with Altitude Training Effect

To determine the mechanism for the beneficial

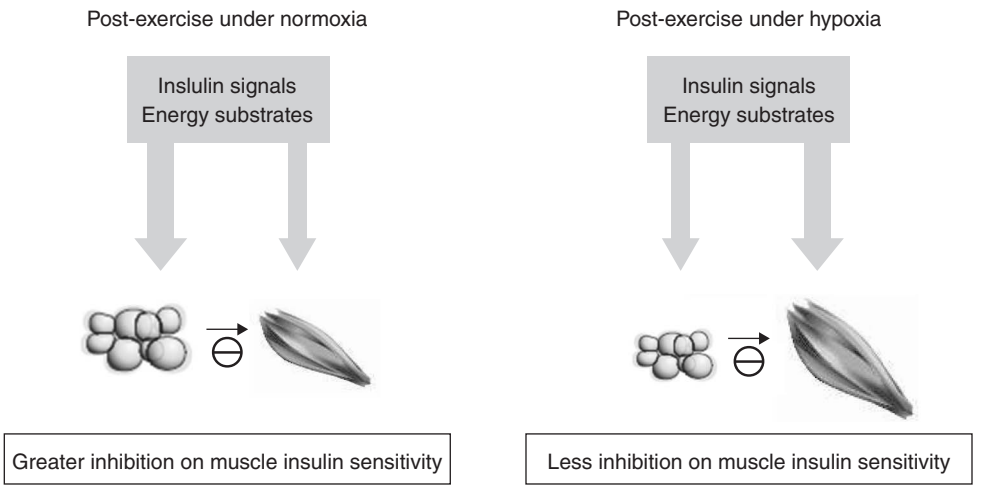
effect of altitude training on insulin sensitivity and glucose tolerance, we performed both animal and human experiments. Similar to obese humans, genetically obese animals exhibit greater fasting insulin levels, and exaggerated glucose and insulin responses following an oral glucose challenge compared with lean counterparts. During a 6-week training period, rats performed swimming exercise progressively from 30 to 180 min/day, and recovered under hypoxia (14% oxygen for 8 h/day). At week 6, body weight, fasting glucose, fasting insulin, area under curve of glucose (GAUC) and insulin (IAUC) were significantly decreased among the obese rats. Capillaries to fiber ratio, capillary density, and type IIa fiber proportion of the plantaris muscle in the exercise-trained group were significantly increased above control level, but no additive effect of hypoxia and exercise training was observed. Our data also demonstrate that exercise training with prolonged hypoxia recovery offers better metabolic benefits than exercise training alone for genetically obese animals. This advantage was closely associated with the effective weight reduction (31). Obesity has been recognized as a major contributor of type 2 diabetes and its metabolic complications (18).

Under insulin-stimulated condition, skeletal muscle accounts for ~85% of glucose uptake (10), thus intervention that affects muscle property may also influence the whole-body glucose tolerance and insulin sensitivity. The effects of altitude training on the AMPK-related glucose transport pathway in skeletal muscle of both lean and obese Zucker rats was studied (9, 31). The skeletal muscle AMP-activated protein kinase (AMPK)-related glucose transport pathway is involved in glucose homeostasis. We found that obese animals have abnormal LKB1-AMPK-AS160-GLUT4 signaling system in red gastrocnemius muscle compared to that in lean (normal) animals. AS160 is a triggering protein factor that commands the GLUT4 translocation from the intracellular pool to the plasma membrane. GLUT4 is responsible for insulin-stimulated glucose transport across plasma membrane in skeletal muscle (9). We compared the chronic training effects of hypoxia training and exercise training on this pathway in lean and obese rats. The obese rats had higher body weights, elevated fasting insulin and glucose levels, and higher baseline levels of muscle AMPK and AS160 phosphorylation compared with those of lean animals. After hypoxia training, the levels of AMPK, AS160 phosphorylation, fasting insulin, and fasting glucose were reversed toward normal concomitant with an approximate 50% increase in the muscle GLUT4 protein level compared with those of the control group. GLUT4 is the protein expressed in skeletal muscle responsible for insulin-stimulated glucose transport, and plays a major role in post-prandial glucose disposal.

In animals, the knowledge of prolonged systemic hypoxia exposure (with or without training) reducing body fat mass (8) and increasing muscle mass (11) has been well-established. Since ambient oxygen for fatty acid oxidation is less available during altitude hypoxia, fat burning cannot be the best explanation for the body fat-reducing effect. In animals, interventions that increases muscle mass lead to significant reduction in body fat mass (29), suggesting that skeletal muscle plays the dominant role in the regulation of fuel storage in fat tissues. Therefore, we hypothesized that greater distribution of circulatory insulin to skeletal muscle can directly alter the deposition of fuel storage (5), and thus influences body composition. Insulin is the main anabolic hormone which stimulates fuel storage and syntheses of glycogen, triglyceride, and protein in skeletal muscle and adipose tissues (24). Withdraw of insulin in animals for only 7 days can lead to marked reductions in fat mass and fat cell diameter at all depots (14). Therefore divergent distribution in circulatory insulin perfusion among tissues would expect to alter storage among energy-storage tissues. Insulin delivery shift can presumably be maneuvered by increasing blood distribution towards skeletal muscle.

Two sets of human experiment were performed to compare the effect of altitude training on muscle and fat masses. For the first experiment, effect of 3-week altitude training on body composition was determined by dual-energy X-ray absorptiometry (DXA) in 10 male swimmers (age: 14.9 ± 0.4 years, BMI: 20.8 ± 0.4 kg/m^2) who regularly completed a fixed training distance of 12.3 km per day. After baseline measurements, all subjects moved from sea-level (Singapore) to altitude (2200 m, Kunming, Yunnan, PRC). They maintain the same training distance at sea-level (all were motivated to complete their daily swimming volume in the shortest possible time). An additional 8 male control subjects (age: 13.0 ± 1.6 years, BMI: 20.5 ± 1.2 kg/m^2) resided at sea-level were recruited to monitor the possible time-to-time variation of DXA measurements on body composition. We found that altitude exposure rapidly decreases fat mass and increase lean mass for youth swimmers maintaining their body weight. Since the overall dietary intake was not apparently changed, energy balance per se cannot be the best explanation for this significant change.

For the second experiment, effect of hypoxia (16%) on blood distribution to skeletal muscle was measured under glucose-ingested condition (insulin-stimulated condition) during the training recovery. We speculated that the fat-reducing effect is related to increased distribution of insulin and energy sub-



Box 1. Possible mechanism for improved glycemic control by altitude training. Exercise training with hypoxia recovery increases greater distribution of fuel and anabolic signals (*i.e.* insulin) to skeletal muscle that reciprocally limits the growth of adipocyte in humans and animals. Increasing fuel storage in adipose tissue is the most common cause of inhibited insulin-stimulated glucose uptake in skeletal muscle. As skeletal muscle accounts for ~85% whole-body glucose disposal, reduced muscle insulin sensitivity due to greater fat storage results in hyperglycemia. Reduced adiposity in conjunction with increased energy reliance on carbohydrate under hypoxia reliance contributes to the improvement in glycemic control by altitude training.

strates towards skeletal muscle for swimmers. Skeletal muscle blood distribution was measured using near infrared spectroscopy (NIRS) to detect changes in hemoglobin concentration under hypoxic (16% oxygen) and normoxic conditions for 90 min after oral glucose ingestion. We evaluated blood distribution under glucose-ingested hyperinsulinemic condition to mimic postprandial state. The increased blood perfusion into skeletal muscle would expect to result in an increased delivery of glucose and insulin into skeletal muscle.

Our data on hemoglobin increases in skeletal muscle fit well with the finding of reciprocal increase in lean mass and decrease in fat mass for all swimmers after altitude exposure. Increasing insulin distribution into skeletal muscle can promote fuel deposition and muscle growth specifically in the region, which will in turn decrease fuel availability to adipose tissue. Insulin is the major anabolic hormone released after carbohydrate meal, which is able to stimulate glucose uptake (20), glycogen synthesis (6, 19), amino acid uptake (4), net protein synthesis (13), cell proliferation, and triglyceride synthesis (24) in insulin-targeted tissues. Therefore, competition between skeletal muscle and adipose tissue for insulin-dependent fuel acquisition plays a key role in regulating body composition. Reduced fat storage after altitude training will have positive influence on the whole-body glycemic control (Box 1).

Concluding Remarks

1. Altitude exposure increases energy reliance on carbohydrate metabolism.
2. Short-term moderate altitude hypoxia can improve glucose tolerance without affecting fasted glucose (or slight increases).
3. Altitude exposure above 4000 M increases physiological stress, elicits discomfort feeling, and leads to insulin resistance.
4. During training recovery, prolonged moderate hypoxia exposure can significantly reduce fat mass with slight increase in muscle mass without affecting body weight for athletes.
5. During a training recovery, moderate altitude exposure increases blood perfusion towards skeletal muscle under glucose ingested hyperinsulinemic state.
6. For genetically obese animals, exercise training with moderate hypoxia recovery can exert potent effect in correcting obese phenotype.
7. Skeletal muscle from genetically obese animals has abnormal LKB1-AMPK-AS160-GLUT4 signaling pathway, which can be reversed by exercise training with moderate hypoxia recovery.

References

1. Alley, D.E., Metter, E.J., Griswold, M.E., Harris, T.B., Simonsick, E.M., Longo, D.L. and Ferrucci, L. Changes in weight at the end of life: Characterizing weight loss by time to death in a cohort study of older men. *Am. J. Epidemiol*. 172: 558-565, 2010.
2. Amsel, J., Waterbor, J.W., Oler, J., Rosenwaike, I. and Marshall, K. Relationship of site-specific cancer mortality rates to altitude. *Carcinogenesis* 3: 461-465, 1982.
3. Baulieu, E.E. and Robel, P. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids. *Proc. Natl. Acad. Sci. USA* 95: 4089-4091, 1998.

4. Biolo, G., Williams, B.D., Fleming, R.Y. and Wolfe, R.R. Insulin action on muscle protein kinetics and amino acid transport during recovery after resistance exercise. *Diabetes* 48: 949-957, 1999.
5. Bonen, A., Clark, M.G. and Henriksen, E.J. Experimental approaches in muscle metabolism: hindlimb perfusion and isolated muscle incubations. *Am. J. Physiol*. 266: E1-E16, 1994.
6. Bouskila, M., Hirshman, M.F., Jensen, J., Goodyear, L.J. and Sakamoto, K. Insulin promotes glycogen synthesis in the absence of GSK3 phosphorylation in skeletal muscle. *Am. J. Physiol*. 294: E28-E35, 2008.
7. Cartee, G.D., Douen, A.G., Ramlal, T., Klip, A. and Holloszy, J.O. Stimulation of glucose transport in skeletal muscle by hypoxia. *J. Appl. Physiol*. 70: 1593-1600, 1991.
8. Chen, H.H., Chen, Y.L., Huang, C.Y., Lee, S.D., Chen, S.C. and Kuo, C.H. Effects of one-year swimming training on blood pressure and insulin sensitivity in mild hypertensive young patients. *Chinese J. Physiol*. 53: 185-189, 2010.
9. Chen, Y.C., Lee, S.D., Kuo, C.H. and Ho, L.T. The Effects of altitude training on the AMPK-related glucose transport pathway in the red skeletal muscle of both lean and obese zucker rats. *High Alt. Med. Biol*. 12: 371-378, 2011.
10. DeFronzo, R.A., Jacot, E., Jequier, E., Maeder, E., Wahren, J. and Felber, J.P. The effect of insulin on the disposal of intravenous glucose. *Diabetes* 30: 1000-1007, 1981.
11. Deveci, D., Marshall, J.M. and Egginton, S. Relationship between capillary angiogenesis, fiber type, and fiber size in chronic systemic hypoxia. *Am. J. Physiol*. 281: H241-H252, 2001.
12. Facchini, F.S., Hua, N., Abbasi, F. and Reaven, G.M. Insulin resistance as a predictor of age-related diseases. *J. Clin. Endocrinol. Metab*. 86: 3574-3578, 2001.
13. Ferrando, A.A., Chinkes, D.L., Wolf, S.E., Matin, S., Herndon, D.N. and Wolfe, R.R. A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. *Ann. Surg*. 229: 11-18, 1999.
14. Ghorbani, A., Varedi, M., Hadjzadeh, M.A. and Omrani, G.H. Type-1 diabetes induces depot-specific alterations in adipocyte diameter and mass of adipose tissues in the rat. *Exp. Clin. Endocrinol. Diabetes* 118: 442-448, 2010.
15. Herbert, J. Neurosteroids, brain damage, and mental illness. *Exp. Gerontol*. 33: 713-727, 1998.
16. Huang, Y., Chen, M., Fang, C., Lee, W., Yang, S. and Kuo, C. A possible link between exercise-training adaptation and dehydroepiandrosterone sulfate- an oldest-old female study. *Int. J. Med. Sci*. 3: 141-147, 2006.
17. Katayama, K., Goto, K., Ishida, K. and Ogita, F. Substrate utilization during exercise and recovery at moderate altitude. *Metabolism* 59: 959-966, 2010.
18. Kopelman, P.G. Obesity as a medical problem. *Nature* 404: 635-643, 2000.
19. Kuo, C.H., Hwang, H., Lee, M.C., Castle, A.L. and Ivy, J.L. Role of insulin on exercise-induced GLUT-4 protein expression and glycogen supercompensation in rat skeletal muscle. *J. Appl. Physiol*. 96: 621-627, 2004.
20. Lai, Y.C., Zarrinpashneh, E. and Jensen, J. Additive effect of contraction and insulin on glucose uptake and glycogen synthase in muscle with different glycogen contents. *J. Appl. Physiol*. 108: 1106-1115, 2010.
21. Larsen, J.J., Hansen, J.M., Olsen, N.V., Galbo, H. and Dela, F. The effect of altitude hypoxia on glucose homeostasis in men. *J. Physiol*. 504: 241-249, 1997.
22. Lee, W.C., Chen, J.J., Ho, H.Y., Hou, C.W., Liang, M.P., Shen, Y.W. and Kuo, C.H. Short-term altitude mountain living improves glycemic control. *High Alt. Med. Biol*. 4: 81-91, 2003.
23. Lee, W.C., Chen, S.M., Wu, M.C., Hou, C.W., Lai, Y.C., Laio, Y.H., Lin, C.H. and Kuo, C.H. The role of dehydroepiandrosterone levels on physiologic acclimatization to chronic mountaineering activity. *High Alt. Med. Biol*. 7: 228-236, 2006.
24. Magkos, F., Wang, X. and Mittendorfer, B. Metabolic actions of insulin in men and women. *Nutrition* 26: 686-693, 2010.
25. Mortimer, E.A., Monson, R.R. and MacMahon, B. Reduction in Mortality from Coronary Heart Disease in Men Residing at High Altitude. *New Engl. J. Med*. 296: 581-585, 1977.
26. Nunez, N.P., Oh, W.J., Rozenberg, J., Perella, C., Anver, M., Barrett, J.C., Perkins, S.N., Berrigan, D., Moitra, J., Varticovski, L., Hursting, S.D. and Vinson, C. Accelerated tumor formation in a fatless mouse with type 2 diabetes and inflammation. *Cancer Res*. 66: 5469-5476, 2006.
27. Schobersberger, W., Schmid, P., Lechleitner, M., von Duvillard, S., Hörtnagl, H., Gunga, H.C., Klingler, A., Fries, D., Kirsch, K., Spiesberger, R., Pokan, R., Hofmann, P., Hoppichler, F., Riedmann, G., Baumgartner, H. and Humpeler, E. Austrian Moderate Altitude Study 2000 (AMAS 2000). The effects of moderate altitude (1,700 m) on cardiovascular and metabolic variables in patients with metabolic syndrome. *Eur. J. Appl. Physiol*. 88: 506-514, 2003.
28. Short, K.R., Vittone, J.L. and Bigelow, M.L. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes* 52: 1888-1896, 2003.
29. Suzuki, M., Doi, T., Lee, S.J., Okamura, K., Shimizu, S., Okano, G. and Fushiki, T. Effect of meal timing after resistance exercise on hindlimb muscle mass and fat accumulation in trained rats. *J. Nutri. Sci. Vitaminol*. 45: 401-409, 1999.
30. Tsai, Y., Chou, S., Lin, Y., Hou, C., Hung, K., Kung, H., Lin, T., Chen, S., Lin, C. and Kuo, C. Effect of resistance exercise on dehydroepiandrosterone sulfate concentrations during a 72-h recovery: relation to glucose tolerance and insulin response. *Life Sci*. 79: 1281-1286, 2006.
31. Wu, M.C., Tsai, Y.L., Huang, C.Y., Kao, C.L., Hou, C.W., Chen, C.Y., Korivi, M., Jean, W.H., Lee, S.D. and Kuo, C.H. Hyperinsulinemia and overweight in obese Zucker rats effectively suppressed by exercise training with hypoxia recovery. *Eur. J. Sport Sci*. I: DOI[10.1080/17461391.2011.606839].
32. Zwain, I.H. and Yen, S.S.C. Dehydroepiandrosterone: biosynthesis and betabolism in the brain. *Endocrinology* 140: 880-887, 1999.