

# HEALTH AND NUTRITION NEWS

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## Prefatory Note

### Roles and expectations for the NIHN as a core institute of nutrition research in Japan



Professor Tsuneyuki OKU

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National Institute of Nutrition (NIN) (later, renamed to National Institute of Health and Nutrition; NIHN) was established in 1920 by Dr. Tadasu Saeki, as a standard-bearer of nutrition improvement. NIN aimed at first to reduce the undernutrition and to enlighten the public nutrition activities. Since these activities were implemented under poor social environment which was quite different from our current affluent society, I am sure that the NIN's existence and social contribution of the institute was highly evaluated.

Furthermore, the NIN implemented various activities and played an important role for the nutrition improvement during the confusing period with serious food shortage after the World War II. Along with the rapid economic growth in 1960s, the nutritional status of population was gradually improved. Consequently, the main health problems shifted from acute malnutrition to chronic diseases, namely, lifestyle-related diseases. And, with an increasing trend of overnutrition, the issue of health promotion began to be more seriously discussed, and then, the focus areas of the nutrition research at the NIN have also been greatly changed. Yet, the NIN's activities have been consistently concerned with the public health nutrition for the nutrition improvement of population since the foundation to date, throughout the periods with different historical background. Institutional reform and the nutrition research, both of which considered the social needs in the field of health science, can be the obvious proofs. The current research target on "nutrition", "exercise" and "dietary supplement" also reflects the needs of age. In my opinion,

the promotion of "recreation and rest" should also be enhanced hereafter.

The recommended dietary allowance (RDA) was established for the first time in 1947. Since then, RDA was revised every five year, for which the NIN has played a core role.

Now, the Dietary Reference Intakes (DRIs) newly established, which was the first revision of RDA after NIHN was transformed into an incorporated administrative agency. Great and unconventional efforts were made by the NIHN to establish DRIs, and I think their contribution for DRIs should worth of being highly evaluated. Likewise, the position of NIHN in the Health Promotion Law (enacted in 2002) also clearly shows its roles for the health and nutrition policy.

While we work on the health problems of population, we can not overlook the nutrition problems. We, nutrition experts, should be more aware that the term of "nutrition" gradually disappears in the various sections of public sectors. For example, there is no longer section with the name of "nutrition" at the Ministry of Health, Labour and Welfare and the Departments focusing on the nutrition research now hardly remain in any national/public/private medical universities.

The NIHN is now only the research institute in the field of nutrition. I believe that its importance of existence should be fully acknowledged by working on the health and nutrition problems of populations very hard and by contributing the nutrition improvement. I therefore expect that the NIHN will continue the efforts for nutrition research aimed at the nutrition improvement of population hereafter too.

## Current Research Projects

### Research on energy metabolism using the human calorimeter

Shigeho Tanaka

Laboratory of Exercise Physiology

Division of Health Promotion and Exercise

In 2000, the first human calorimeter in Japan was introduced in our Institute (see **Photo**). Human Calorimeter enables us to measure accurate 24-h energy expenditure (TEE), as well as energy expenditure at rest, during sleeping and of various activities, by measuring the changes of O<sub>2</sub> and CO<sub>2</sub> concentration while a study subject stays in the human metabolic chamber.

So far, the following two types of methods were generally applied to measure energy expenditure;

- a) Calculation of energy expenditure from the measured O<sub>2</sub> intake, for which a subject is asked to wear a face mask etc.
- b) Estimation of energy expenditure using the relational formulae with O<sub>2</sub> intake, by wearing heart rate monitor, accelerometer or recording the activities.

Although the energy expenditure can be measured quite accurately by the method a), there are two major limitations; one is that measuring condition greatly differ from the actual daily life, and the other is that it is impossible to measure for long hours. On the other hand, the method b) is absolutely indirect one and that there is a limitation with the accuracy for the estimation of low-intensity activities while these activities take up most of the day.



Now, these problems have been sorted out by the introduction of human calorimeter, as its measurement error can be kept within  $\pm 1\%$  (quite lower than that of earlier methods) for long hours, even for several days, by checking it with regular alcohol combustion test. Furthermore, it is also possible to estimate the expended energy sources (e.g. carbohydrate, lipid, protein).

By using this human calorimeter, we are currently working on the following researches;

#### 1) *Energy expenditure and physical activity levels for the specified activities*

The energy expenditure for a daily life with typical physical activity was measured by the human calorimeter. As a result, it was explored that the prediction by the method described in the latest 6<sup>th</sup> Recommended Dietary Allowance (RDA) for Japanese would underestimate the actual energy expenditure and physical activity levels.

#### 2) *Development of methods to assess the energy expenditure and physical activity level*

As is written in the above, it is quite difficult to measure the energy expenditure at the daily life, especially the low-intensity activities (e.g. activities while sitting). Under this circumstance, in addition to the activity diary method (All the activities are recorded and predicted energy expenditure of each activity is applied to calculate TEE), we are currently working on the development of a new method to explore the details of low-intensity activities.

If this attempt succeeds, the amount and contents of physical activity in daily life can be assessed more accurately and objectively. We can also expect that it will be useful to determine, for example, the effects of physical activity on obesity and impact of exercise prescription.

# Thoughts on Health and Nutrition Research

## General term, scientific term and legal term

Mamoru Nishimuta  
Division of Human Nutrition

Topics on nutrition are discussed among not only nutrition experts but also general public. The use of specific “term”, however, can often be a barrier in the discussion. For example, when “mineral” is used as a general term, the interpretation of “mineral” is not always same between the speaker and the listener. If somebody asks “What’s mineral?”, many of us would get stuck for answer. Since there is no strict definition of “mineral” even as a scientific term, we need to apply a certain definition when “mineral” is used as a scientific term. So, it should be like;

“In this paper, `minerals` is used as a collective term of elements except for hydrogen (H), carbon (C), nitrogen (N) and oxygen (O)”

On the other hand, we normally proceed with the general discussion without confirming the definition of “term”, which often leads to the above mentioned confusion. “Mineral water” is also a general term, and it is not surprising that some people may believe it contains relatively lots of minerals. In this case, sodium (Na) is not recognized as a mineral while it is actually a mineral if the above scientific definition is applied here.

So, there may arise a serious argument, accusing that “This mineral water has false labeling, because it contains little minerals”. However, in this argument, the discussion is made on science or law using the undefined term. It is therefore necessary to confirm the definition of term first, so as to start scientific discussion.

As for legal term, the definition is clarified by law. “Foods for Specified Health Use” and “Food with nutrient function claims” are legal terms and thus, the definition is clearly specified. How about “nutritional supplementary food”, then? Since this is a general term, the interpretation may vary by

each person. So, we can say that the argument on “What’s nutrition support food?” actually does not make sense.

“Health food” is also a general term. Well, what’s the difference between “food” and “health food”? This is also a nonsense argument, but why these foods are named with “health”? Apparently, it is likely that sales companies intended to use the positive image on “health” among consumers who believe “health food” is more beneficial than “food”. Sadly, some of them would even expect the pharmacological effects of “health foods”. In reality, labeling the pharmacological effects on “food” is against the Pharmaceutical Affairs Law. So, generally, no sales company declares the pharmacological effects on foods for marketing.

As for “Foods for Specified Health Use”, the pharmacological effects of certain components are officially acknowledged. Yet, we still need to be careful to declare its effects in the food label. For example, for “Foods for Specified Health Use” containing components with antihypertensive effects, it is not allowed to put the label like “This food is effective for the treatment of hypertension”. Instead, the description on the label should be like “This food is recommended for those who are concerned about own blood pressure”.



### Ovariectomy in mice decreases lipid metabolism related gene expression in adipose tissue and skeletal muscle with increased body fat

Yasutomi Kamei (Division of Clinical Nutrition)

When the energy intake from foods exceeds the energy expenditure by exercise, energy is accumulated as body fat. It has been known that women are likely to be obese after menopause, due to a lack of estrogen. Ovariectomy in rodents is the most reliable way of expressing menopause in the animal model. Since the ovary is the main organ that produces estrogen, the symptoms after ovariectomy could be similar to those after menopause. Previous studies have shown that bone density decreased in ovariectomized mice, leading to osteoporosis as in postmenopausal women. In addition, weight gain is also observed among these mice. Ovariectomy-induced obesity in mice is associated with a decrease in oxygen consumption, indicating repressed energy expenditure. Yet, no study has explored the precise nature of this decrease in energy expenditure. Skeletal muscle is an important organ for energy expenditure, and in mice, adipose tissue is also involved. In this study, to elucidate the mechanism of weight gain after ovariectomy, we examined the expression patterns of genes related to energy expenditure and lipid metabolism in adipose tissue and skeletal muscle. At 2-4 wk after ovariectomy, levels of nuclear receptors and cofactors involved in energy expenditure such as ERR1, PPAR  $\alpha$  and PPAR  $\delta$ , and PGC1  $\alpha$  and PGC1  $\beta$  were lower than those in control mice. mRNA levels of their targets, medium-chain acyl coenzyme A dehydrogenase and acetyl CoA oxidase, enzymes for fatty acid  $\beta$ -oxidation, also decreased. When fatty acid  $\beta$ -oxidation, a channel to resolve the fatty acid, is active with high levels of enzymes for fatty acid  $\beta$ -oxidation, body fat is expended as energy. On the contrary, ovariectomized mice had low levels of enzymes for fatty acid  $\beta$ -oxidation, and thus, body fat is not expended well. Therefore, changes of gene expression observed in this study could explain the obesity in ovariectomized mice. That is, a decrease in the expression of energy expenditure-related genes in adipose tissue and skeletal muscle could be, in part, responsible for obesity after ovariectomy. Further study should provide more insight into molecular mechanism of OVX-induced obesity, which could be of medical importance for weight gain among postmenopausal women.



In skeletal muscle and adipose tissue (see Figure), nuclear receptors (e.g. ERR, PPAR) and cofactors (e.g. PGC  $\alpha$ , PGC  $\beta$ ) control the expression of genes related to energy expenditure and lipid metabolism. Ovariectomy in mice decreases the expression of these genes: hence, the decrease of energy expenditure, possibly leads to weight gain.

### Ovariectomy in mice decreases lipid metabolism-related gene expression in adipose tissue and skeletal muscle with increased body fat.

Journal of Nutritional Science and Vitaminology. 2005;51(2):110-117.

Kamei Y<sup>1-3)</sup>, Suzuki M<sup>1)</sup>, Miyazaki H<sup>1)</sup>, Tsuboyama-Kasaoka N<sup>1)</sup>, Wu J<sup>1)</sup>, Ishimi Y<sup>1)</sup> and Ezaki O<sup>1)</sup>

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**Abstract:** Postmenopausal women as well as rodents after ovariectomy, which results in a lack of estrogen, can become obese. Ovariectomy-induced obesity in mice is associated with a decrease in oxygen consumption, indicating repressed energy expenditure. In this study, to elucidate the mechanism of weight gain after ovariectomy, we examined the expression patterns of genes related to energy expenditure and lipid metabolism, in mouse tissues including adipose tissue and skeletal muscle. In adipose tissue and skeletal muscle, at 2-4 wk after ovariectomy, levels of nuclear receptors and cofactors involved in energy expenditure such as ERR1, PPAR  $\alpha$  and PPAR  $\delta$ , and PGC1  $\alpha$  and PGC1  $\beta$  were lower than in control mice. mRNA levels of their targets, medium-chain acyl coenzyme A dehydrogenase and acetyl CoA oxidase, enzymes for fatty acid  $\beta$ -oxidation, were lower. In addition, the expression of PPAR  $\gamma$  and SREBP1, transcription factors important for lipogenesis, was decreased, as well as that of acetyl CoA carboxylase and fatty acid synthase, enzymes for fatty acid synthesis, and diacyl glycerol acetyl transferase 1 and 2, enzymes for triglyceride synthesis. These changes in gene expression are consistent with the obese phenotype in mice after ovariectomy. Thus a decrease in the expression of energy expenditure-related genes in adipose tissue and skeletal muscle could, in part, be responsible for obesity after ovariectomy.

## Latest Research

### Effects of alcohol consumption on the diabetics among middle-aged Japanese.

Masako Tanaka (Division of Health Informatics and Education)

Japanese immigrants living in the United States and Brazil have acquired a westernized lifestyle, but their generic background is regarded still same as Japanese. Since the prevalence of type 2 diabetics among the immigrants is higher than that of Japanese, it is plausible that Type 2 diabetics is associated with a generic predisposition, but is also strongly influenced by life-style related factors such as diets and/or physical activity. Over the past decades, however, the prevalence of diabetes has increased dramatically in Asian countries, including Japan. Prevention of diabetes through improvement of lifestyle is therefore an urgent health issue in this area. For which, it is important to investigate whether the risk factors identified in western populations could also apply to Asian ethnic groups. So far, few studies have attempted to answer this question. This study, therefore, aimed to quantify the risk factors for diabetes in a general Japanese population by a prospective cohort study (Japan Public Health Center-based prospective study on cancer, cardiovascular diseases: JPHC study). Total of 28,893 individuals (12,913 men and 15,980 women) without history of diabetes and cardiovascular diseases participated in this study. Following the baseline questionnaire completed in 1990, follow-up questionnaires were sent to each participant in 1995 and 2000. These self-administered questionnaires included the questions on; weight, height, usual physical activity patterns, smoking habits, alcohol intake (items, frequency per week, amount consumed daily), previously diagnosed medical conditions, family history of diabetes and other lifestyle-related factors. As for alcohol intake, the subjects were classified into two groups: "non drinkers and infrequent occasional drinkers" and "drinkers". And, "drinkers" were further subdivided into three groups by daily ethanol consumption. During the 10-years follow-up, 703 men and 482 women reported newly diagnosed diabetics. Multivariate logistic regression revealed that age, BMI, family history of diabetes and smoking were significant factors for diabetes in both genders. As for alcohol consumption, whilst no significant association was observed for women and men with BMI > 22kg/m<sup>2</sup>, moderate/high alcohol consumption showed high risk of developing diabetes for men with BMI ≤ 22kg/m<sup>2</sup>. Studies conducted in the United states and Europe showed an inverse correlation between alcohol intake and Type 2 diabetes or suggested no significant association. On the other hand, a few study showed an excess diabetes incidence only in heavy drinkers. Therefore, the association between alcohol intake and diabetes remains uncertain. Yet, our findings would suggest that alcohol consumption might have more adverse effect on development diabetes for Japanese, in comparison with western populations. This may be due to the difference in distribution of polymorphic ethanol-metabolizing enzymes between Japanese and western populations.

### Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I.

Diabetic Medicine. 2005;22(3):323-331

Waki K, Noda M, Sasaki S, Matsumura Y, Takahashi Y, Isogawa A, Ohashi Y, Kadowaki T and Tsugane S for the JPHC study group

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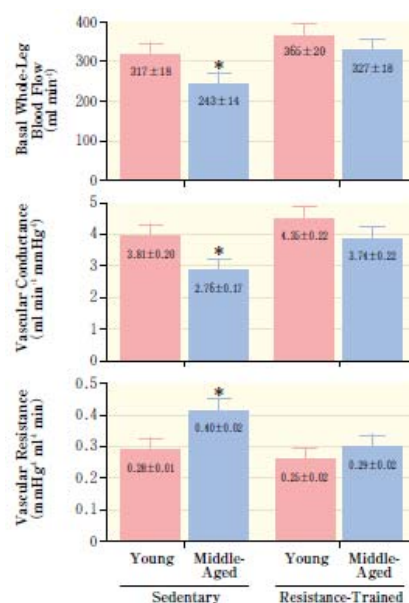
#### Abstract:

**AIMS:** Few prospective studies have examined the relationship between lifestyle characteristics and the incidence of diabetes mellitus in an Asian general population. This study was undertaken to evaluate the risk factors for Type 2 diabetes in a population-based prospective study of middle-aged Japanese. **METHODS:** We investigated 12,913 men and 15,980 women, aged 40-59 years at baseline (year 0), who participated in the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort I. The participants were followed for up to 10 years. Incident cases of diabetes were identified by self-reporting of a physician's diagnosis on two questionnaires sent to each participant, one at year 5 and the second at year 10. **RESULTS:** During the 10-year follow-up, 703 men and 482 women reported newly diagnosed diabetes. Age, body mass index (BMI), family history of diabetes and cigarette smoking were independent risk factors in both genders by multivariate analysis. Among men with a BMI ≤ 22 kg/m<sup>2</sup>, a significant positive association was observed between the diabetes incidence and moderate (23.0 < 46.0 g/day) to high (> 46.0 g/day) alcohol consumption, odds ratio 1.91 (95% CI, 1.05-3.46) and 2.89 (1.63-5.11), respectively. Among men with a BMI > 22 kg/m<sup>2</sup>, a small non-significant increase in odds ratio was observed with alcohol consumption. **CONCLUSIONS:** Established risk factors for diabetes in western populations were also identified as predictors of the disease among Japanese. Moderate to high alcohol consumption was positively associated with the incidence of diabetes in Japanese lean (BMI ≤ 22 kg/m<sup>2</sup>) men.

**Lack of age-related decreases in basal whole-leg blood flow in resistance-trained men.**

**Motohiko Miyachi (Division of Health Promotion and Exercise)**

Reductions in basal leg blood flow, which decrease progressively with advancing age, have been implicated in the pathogenesis of metabolic syndrome and functional impairment in human. Regular physical activity is important for the prevention and treatment of cardiovascular disease and functional ability. Yet, previous studies show that habitual aerobic exercise does not modulate the age-related reductions in basal leg blood flow in healthy men. On the other hand, resistance training is known to be effective to prevent the age-related loss in muscle mass and function (e.g. sarcopenia). This study therefore aimed to determine the relation between resistance training, leg muscle mass and basal leg blood flow. We hypothesized that resistance training is associated with elevated leg perfusion in aging humans through its impact on leg skeletal muscle mass. A total of 104 healthy men aged 20-34 years (young) and 35-65 years (middle-aged) participated in this study. Half of them were the resistance-trained men who had been performing vigorous resistance training for > 2 years, and the other half were sedentary subjects who had not participated in any regular exercise program for at least the previous 2 years. All the subjects were normotensive (<140/90mmHg), nonobese and free of overt chronic diseases as assessed by medical history, physical examination and blood test. A duplex ultrasound machine equipped with a high resolution linear-array transducer was used to measure vessel diameter and blood velocity on the right common femoral artery. This study confirmed that the age-associated reduction in basal whole leg blood flow did not occur in resistance trained men, implicating that daily weight training may prevent diseases in basal whole blood flow with advancing age. These results therefore suggest that habitual resistance exercise may favorably influence leg perfusion and hemodynamics in the aging human. Although it is well known that abdominal fat accumulation is underlying mechanism for metabolic syndrome and diabetes, the risk of atrophy in skeletal muscle (principal organ for energy expenditure) also should not be ignored. As is well known, it is essential to increase the physical activity and exercise, so as to prevent metabolic syndrome and diabetes. While many people are aware of the effects of aerobic exercise (e.g. walking), it is important to pay attentions to the effects of resistance training as well.



**Lack of age-related decreases in basal whole-leg blood flow in resistance-trained men.**

**Journal of Applied Physiology.** 2005;99(4):1384-90

**Miyachi M, Tanaka H, Kawano H, Okajima M and Tabata I.**

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**Abstract:** Reductions in basal leg blood flow have been implicated in the pathogenesis of metabolic syndrome and functional impairment in humans. We tested the hypothesis that reductions in basal whole leg blood flow with age are either absent or attenuated in those who perform regular strength training. A total of 104 normotensive men aged 20-34 yr (young) and 35-65 yr (middle aged), who were either sedentary or resistance trained, were studied. Mean and diastolic blood pressures were higher ( $P < 0.05-0.001$ ) in the middle-aged compared with the young men, but there were no significant differences between the sedentary and resistance-trained groups. In the sedentary group, basal whole leg blood flow (duplex Doppler ultrasound) and vascular conductance were lower (approximately 30 and approximately 38%, respectively;  $P < 0.01$ ) in the middle-aged compared with the young men. There were no such age-related differences in the resistance-trained group. In the young men, basal whole leg blood flow and vascular conductance were not different between the two activity groups, but, in the middle-aged men, they were higher (approximately 35 and approximately 36%, respectively;  $P < 0.01$ ) in the resistance-trained men than in the sedentary men. When blood flow and vascular conductance were expressed relative to the leg muscle mass, the results were essentially the same. We concluded that the age-related reduction in basal whole leg blood flow is absent in resistance-trained men. These results suggest that resistance training may favorably influence leg perfusion in aging humans, independent of its impact on leg muscle mass.

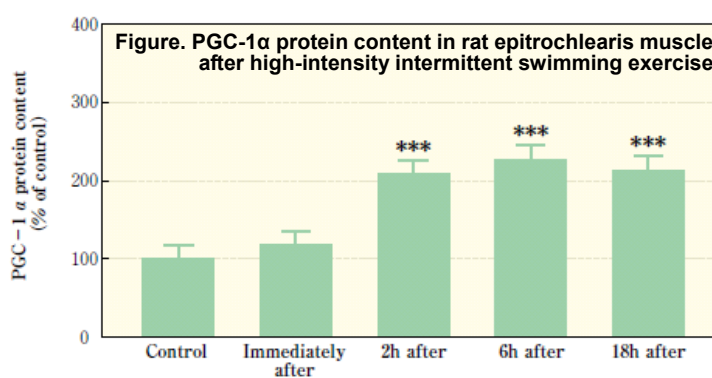
## Effects of high-intensity exercise on PGC-1 $\alpha$ protein expression

Izumi Tabata (Division of Health Promotion and Exercise)

It is well known that physical training increases the glucose metabolism and the physical endurance, and also promotes the energy metabolism. In this way, many adaptive responses to physical training can be observed concurrently in skeletal muscle. It has been regarded that this phenomena is due that exercise would stimulate a gene or more, which develop the expression of several proteins, rather than due that stimulus of exercise would affect each gene of protein which increased and became bioactive by exercise.

Recent studies have shown that PGC-1 $\alpha$  (peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$ ) protein is involved in both GLUT-4 expression (which is associated with glucose metabolism in muscle, hence, with diabetes) and mitochondrial proteins (which is associated with endurance and energy metabolism, hence, with obesity). PGC-1 $\alpha$  is one of the transcriptional coactivators (which promote the smooth transcription from DNA to mRNA), and it is said that a person with low expression of PGC-1 $\alpha$  is at high risk of developing diabetes. It is also reported that physical endurance is influenced by the difference in the genetic factor of PGC-1 $\alpha$ . That is, PGC-1 $\alpha$  is a possible master key that would influence the transcription of many genes and increase the expression of many proteins. We therefore hypothesized that PGC-1 $\alpha$  might be related to the increase of protein expression during the exercise, and then confirmed for the first time that PGC-1 $\alpha$  would increase by the exercise/physical training.

This time, in the following article, we explored that high-intensity intermittent exercise, like speed skaters would practice, could increase PGC-1 $\alpha$  expression in skeletal muscle to the level observed after low-intensity prolonged exercise. These findings would suggest that high-intensity exercise can be as effective as low-intensity exercise, in terms of the increase of GLUT-4 and mitochondria. Therefore, the high-performance sports with high possibility of continuation can be recommended for the prevention of diabetes and obesity.



## Effects of high-intensity intermittent swimming on PGC-1 $\alpha$ protein expression in rat skeletal muscle.

*Acta Physiologica Scandinavica*, 2005; 184(1):59-65

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### Abstract:

**AIM:** The aim of the present investigation was to elucidate the effects of exercise intensity on exercise-induced expression of peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) protein in rat skeletal muscle. **METHODS:** We measured PGC-1 $\alpha$  content in the skeletal muscles of male Sprague-Dawley rats (age: 5-6 weeks old; body weight: 150-170 g) after a single session of high-intensity intermittent exercise (HIE) or low-intensity prolonged swimming exercise (LIE). During HIE, the rats swam for fourteen 20-s periods carrying a weight (14% of body weight), and the periods of swimming were separated by a 10-s pause. LIE rats swam with no load for 6 h in two 3-h sessions, separated by 45 min of rest. **RESULTS:** After HIE, the PGC-1 $\alpha$  protein content in rat epitrochlearis muscle had increased by 126, 140 and 126% at 2, 6 and 18 h, respectively, compared with that of the age-matched sedentary control rats' muscle. Immediately, 6 and 18-h after LIE, the PGC-1 $\alpha$  protein content in the muscle was significantly elevated by 84, 95 and 67% respectively. The PGC-1 $\alpha$  protein content observed 6 h after HIE tended to be higher than that observed after LIE. However, there was no statistically significant difference between the two values (P=0.12). **CONCLUSION:** The present investigation suggests that irrespective of the intensity of the exercise, PGC-1 $\alpha$  protein content in rat skeletal muscle increases to a comparable level when stimuli induced by different protocols are saturated. Further, HIE is a potent stimulus for enhancing the expression of PGC-1 $\alpha$  protein, which may induce mitochondrial biogenesis in exercise-activated skeletal muscle.