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Full Length Research Paper

Transcriptional peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α) regulates transformation of muscle fiber type in *Schizothorax prenanti*

Yaqiu Lin[1#]*, Ruiwen Li[2#], Yucai Zheng [1], Runfeng Zhang[3], Juchun Lin[4] and Xiang Qiu[1]

[1]College of Life Science and Technology, Southwest University for Nationalities, Chengdu, Sichuan 610041, China.
[2]Reproductive and Endocrine Laboratory, Chengdu Woman-Child Central Hospital, Chengdu Sichuan 610091, China.
[3]College of life science, Hubei Normal University, Huangshi, Wuhan 435002, China.
[4]College of Animal Medicine, Sichuan Agricultural University, Yaan, Sichuan 625014, China.

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Peroxisome proliferator-activated receptor γ coactivator (PGC)-1α, a well-known member of PGC-1 transcriptional coactivator's family, plays a key role in various metabolic pathways. Here, we investigated the role of PGC-1α in the transformation of muscle fiber type in *Schizothorax prenanti*. The expression of PGC-1α was induced in *S. prenanti* muscles following fasting. Following the induction of PGC-1α, the expressions of mitochondrial-related enzyme cytochrome c oxidase (COX), citrate synthase (CS) and cytochrome c oxidase IV was also increased in white muscles, but the expression of carnitine palmitoyltransferase II (CPT II) has no change in this condition. Notably, when the levels of PGC-1α was upregulated in the condition of fasting, muscle fibres type II showed the characteristics of muscle fibres type I, with expressed myosin heavy chain I (MyHC I) and myoglobin (Mb), and suppressed myosin heavy chain II (MyHC II) in response to fasting. Therefore, we can draw conclusion that PGC-1α up-regulates slow fiber type formation during the transformation of muscle fiber type in *S. prenanti*.

Key words: PGC-1α, muscle fiber type, transformation, *Schizothorax prenanti*, MyHC I, MyHC II.

INTRODUCTION

Muscle fiber, a key determinant of meat quality, is affected by few environmental factors and general biochemical properties. Many differences exist in contraction, mitochondrial composition and mitochondrial oxidative capacity in different muscle fibers (Berchtold et al., 2000) which results in different qualities (Picard et al., 2006). Two main fiber types (types I and II) can be distinguished by the morphology, function, and the physiological and biochemical properties in mammals. All three fast myosin heavy chains (*MyHC*) genes were expressed in the skeletal muscle and MyHCs are considered as the best markers for the identification of muscle fibers at present. Studies in mammals demonstrated that meat with high type I fiber is more tender, redder and succulent with good taste, compared to meat with high type II fiber (Lefaucheur et al., 2004; Bowker et al., 2004). Therefore, induction of the conversion of type II fibers into I type fibers will provide an efficient approach to improve meat

*Corresponding author. E-mail: linyaqiu0001@yahoo.com.cn.

Abbreviations: PGC-1α, Peroxisome proliferator-activated receptor γ coactivator-1; **COX,** cytochrome c oxidase; **CS,** citrate synthase; **CPT II,** carnitine palmitoyltransferase II; **MyHC I,** myosin heavy chain I; **MyHC II,** myosin heavy chain II; **Mb,** myoglobin; **MEF-2,** myocyte-specific enhancer factor 2; **PPARγ,** peroxisome proliferator-activated receptors δ; **HIF-1α,** hypoxia-inducible factor-1α; **HIF-2α,** hypoxia-inducibly factor -2; **FOXO1,** forkhead box1; **Sirt1,** sirtuin 1.

#These authors contributed equally to this paper

quality traits.

The coactivator PGC-1α, a member of PGC-1 family, is a master regulator of energy metabolism. PGC-1α is identified as a nuclear receptor coactivator that interacts with peroxisome proliferator-activated receptors (PPAR)-γ, and plays a key role in linking nuclear receptors to the transcriptional programs of adaptive thermogenesis and oxidative metabolism (Puigserver et al., 1998). Some specific factors such as cold, fasting and exercise can induce the expression of PGC-1α. After induction, PGC-1α mediates multiple biological processes by altering activities of different transcription factors in different tissues. Available evidence suggested that PGC-1α plays an important role in the conversion of muscle fibers in mammals. PGC-1α could induce the switch between muscle fiber types I and II in a transgenic mice model (Lin et al., 2002). In PGC-1α transgenic mice, the type II fiber has similar characteristics with type I fiber and the oxidative capacity of mitochondria was also enhanced, suggesting that the expression of some type I fiber-specific proteins was induced. Furthermore, there are many studies in human, mouse and chicken using different method (Ueda et al., 2005; Handschin et al., 2007; Geng et al., 2010; Yamaguchi et al., 2010). The results indicate that transformation mode of PGC-1α is species-specific.

There are some differences between muscle fibers in fish and mammal, such as short muscle fibers, loose structral organization of proteins and higher water content in fish. However, muscle fibers in fish are also composed of red and white muscle similar to mammalian muscle. Muscle growth in fish, including red and white muscle, is of independent existence (Ferna´ndez and Calvo, 2009). Also, it is easy to distinguish muscle type switching and remodeling in fish. Therefore, fish can be a better research model for conversion of muscle fibers type. Similar to mammalian skeletal muscle, the fiber-type switching has also taken place in fish in response to the change of environmental factors, such as nutrition (Sänger and Stoiber, 2001; Johnston, 2001). However, these studies have not been involved in the functions of gene regulation in fiber-type switching. So far, the role of PGC-1α in the process of fiber-type switching in fish is not yet reported.

Schizothorax prenanti is a unique fish in Tibet plateau in China. Due to the fact that its meat contains such advantages as tender, meaty delicious, rich in fat, especially rich in lysine which can compensate for the lack of human dietary intake of lysine, it becomes the main edible fish of the local residents. In the present study, we used *S. prenanti* as a model to study the conversion of muscle fiber. After induction of *PGC-1*α gene expression by fasting, the expression of genes involved in muscle fiber and mitochondrial-related enzyme in red and white muscle were analyzed to reveal the functions of PGC-1α on muscle fibers type switching in *S. prenanti*.

Our results will provide important theoretical basis for quality improvement of fish, and also genetic improvement and breeding of fish.

MATERIALS AND METHODS

Sampling of *S. prenanti*

Adult *S. prenanti* (500 ± 12 g) were collected in Yaan, Sichuan Province, China and then acclimated for approximately one week in dechlorinated tap water at constant water temperature 20°C on average, and fed daily with cold-water fish chow (Chengdu, Sichuan Province, China). The condition stated above was for control group during the experiment. Experimental group was held without being fed. Fish were analysed at the end of the second week for samples needed for histochemistry. The fish were killed by a single blow to the head and muscle sections were obtained. The sections were immediately frozen in liquid N_2-cooled isopentane as described previously (Dubowitz, 1985). For gene expression, the fish were killed as described above, and the red and white muscles were rapidly excised and frozen in liquid N_2.

Gene expression

Total RNA was extracted from *S. prenanti* red and white muscles, using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Purity and concentration of RNA was determined spectrophotometrically by measurement of UV absorbance at 260 and 280 nm, and RNA was stored at -80°C for future use. Then, 1 μg of total RNA was subjected to the cDNA synthesis in 12 μl reaction volume. The oligo-dT primed cDNA synthesis was performed with first strand cDNA synthesis kit (Fermentas Life Science, Hanover, MD, US) according to manual instruction. The expression level of each gene was determined by quantitative real-time RT-PCR method. The PCR primers were designed using Primer Premier 5 software based on the sequences of target gene of *S. prenanti* ,*Danio rerio* and common carp (Table 1). Real-time (RT) analysis was performed on a fluorescence temperature icycler (Bio-Rad, Hercules, CA, USA) using the following conditions: an initial denaturation for 1 min at 95°C, followed by 40 cycles of 30 s denaturation at 95°C, then 30 s annealing at optimal primer temperature (Table 1) and 30 s extension at 72°C. The amplification mixture contained 1 μl of RT reaction mix, 10 μl of SYBRα Premix Ex Taq TM (2×) (TaKaRa, Dalian, China), 0.5 μl of 10 μmol/l each of primers and additional ddH_2O to 20 μL. The threshold cycle (CT) resulting from RT-PCR was analyzed using the $2\text{-}\Delta\Delta^{Ct}$ method (Livak and Schmittgen, 2001).

Enzyme activities analyses

Approximately 20 mg of powdered tissue was homogenized in 20 volumes of extraction buffer (20 mmol Hepes, 1 mmol ethylenediaminetetraacetic acid (EDTA), 0.1% Triton X-100, pH 7.4) with a ground glass tissue homogenizer on ice. The activities (in U g^{-1}) of cytochrome c oxidase (COX), citrate synthase (CS) were assayed in these crude homogenates at 25°C as previously described (McClelland et al., 2005).

Histological analysis

ATPase-stained was determined by the methods of Ogilvie and Feeback (1990). Muscle samples were frozen in liquid nitrogen-cooled isopentane, and transverse serial sections were stained with ATPase.

Table 1. Primer sequences used for real-time PCR analysis of mRNA expression in *S. prenanti.*

Gene	Forward primer	Reverse primer	Amplicon size (bp)	Annealing temperature
PGC-1α JN195738	gaagatagatgaggaaaatgaggc	atcactggcattggtcacg	133	56.8
COX IV NM_214701	ctacggcatttcgtcttgtt	tcccttctctttctccttgag	194	55.5
CPT II NM_001007447	tgaccccaaacccgaata	tgtaggctccaaaccacgat	200	56.5
MyHC I (sMyHC) AY333451	tctaacctgggcaagttccg	atggcttcacaacaaacaaactc	178	58.6
MyHC II (fMyHC) AF165817	atgagaaccttcgccagataaa	gccagtgcgttcttagcctt	199	58.6
Myoglobin DQ338464	atgctggggagccattgag	ttcagcacagtcgcaccgt	171	56.7
β-actin M24113	gattcgctggagatgatgct	cgttgtagaaggtgtgatgcc	219	54.5

Statistical analysis

Statistical analysis of differences among treatment means were carried out by analysis of variance (ANOVA) (software: SPSS11.5; SPSS, Chicago, IL, USA). Differences were considered statistically significant if $P < 0.05$.

RESULTS

Induction of PGC-1α mRNA expression in response to fasting

We investigated PGC-1α mRNA expression in red and white muscle of fish after fasting for two weeks by real-time PCR. Compared with control group, PGC-1α mRNA level was significantly higher by 3.03 and 4.58-fold in red and white muscle, respectively due to fasting ($P < 0.05$) (Figure 1). This suggested that PGC-1α was induced in *S. prenanti* red and white muscles under fasting condition.

Mitochondria enzyme activities and the related genes expression

To investigate the effects of PGC-1α gene over-expression on mitochondrial related enzyme activities and gene expression, we analyzed the maximal activity of citrate synthase (CS), a key enzyme in the krebbs cycle, and cytochrome c oxidase (COX), a terminal electron acceptor in the electron transport chain. Cytochrome c oxidase (COX) IV and carnitine palmitoyltransferase II (CPT II) mRNA levels in the red and white muscle of *S. prenanti* were also detected during fasting treatments. In red muscle, the activity of the CS and COX increased, but had no significant difference compared with the control group; whereas, in white muscle, the activity of the CS and COX were approximately 1.48 and 1.21-fold higher, respectively than control group ($P < 0.05$) (Figure 2). In white muscle, COX IV mRNA level was induced, but CPTII did not change significantly in response to fasting compared to control group (Figure 3). These results indicate that the over-expression of PGC-1α significantly increased the activities of mitochondrial related enzymes CS and COX in white muscle and promoted the expression level of *COX IV* gene.

Muscle fiber types

The type I muscle fibers are darkly stained, and type II muscle fibers are lightly stained when ATPase was stained at pH 4.3. The results show that relative proportions of the type I fiber were not changed in red muscle. The type I fiber characteristics were observed in the white muscle and type II fibers decreased (Figure 4). We also observed the expression of muscle fiber genes (MyHCI, MyHCII, Mb) in red and white muscle. The results indicate that these genes expression had no significant change in red muscle. In white muscle, the expression of MyHCI (slow) and myoglobin (Mb) increased, and MyHCII (fast) expression decreased (Figure 5).

DISCUSSION

PGC-1α is an important regulator of many metabolic pathways, including adaptive thermogenesis (Puigserver et al., 1998), mitochondrial biogenesis (Ventura-Clapier et al., 2008), fiber-type switching (Lin et al., 2002; Yan et al., 2011), glucose/fatty-acid metabolism (Zhu et al., 2009) and heart development (Sihag et al., 2009). The role of PGC-1α in energy metabolism in aquatic animals was reported by several investigators; however, the function of PGC-1α in the switch of muscle fiber is still unclear. The oxidative capacity of white muscle from Zebra fish was enhanced after one week's training, while PGC-1α expression in red and white muscle increased; it is not involved in switch of muscle fiber type (LeMoine et al., 2010). PGC-1α is strongly expressed in tissue-specific patterns in high metabolic tissues, such as BAT, heart, skeletal muscle, kidney, and brain (Handschin, 2010). Lin showed that PGC-1α is expressed preferentially in muscle enriched in type I fibres (Lin et al., 2002).

In the present study, expression of PGC-1α in

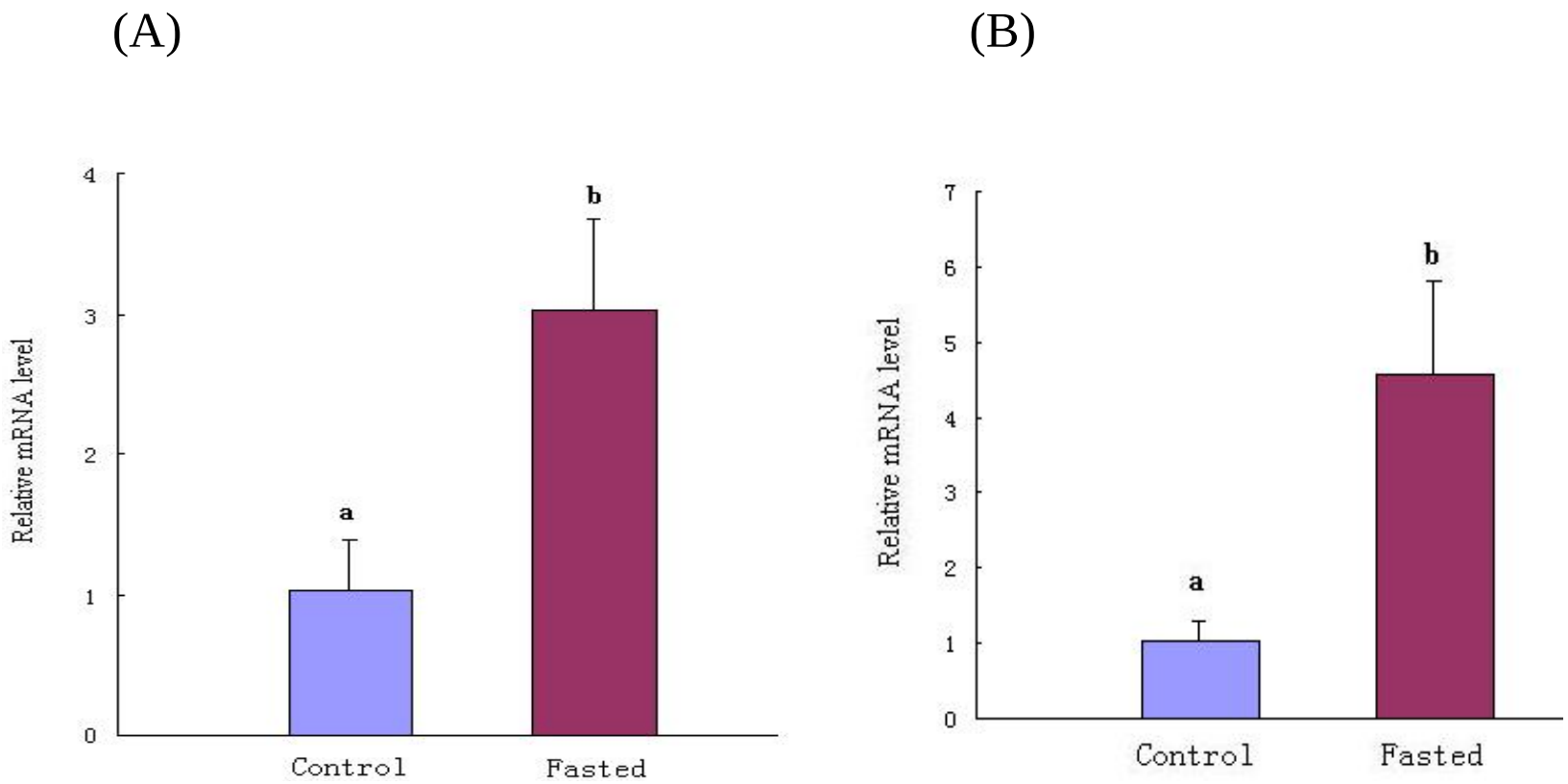

Figure 1. PGC-1α expression in red muscle (A) and white muscle (B) of *S. prenanti* exposed to fasting. Data represents the mean values ± SD of eight replicates; values with different letters indicating significant difference ($P < 0.05$).

mitochondria-rich red muscles of *S. prenanti* in basal metabolism status was significantly higher than white muscles (data not shown).

The expression of PGC-1α can be induced by some specific factors such as cold, fasting and exercise (Knutti and Kralli, 2001). Continuous mild heat stress (CMHS) induces a fast-to-slow fiber-type shift of mammalian myoblasts through PGC-1α dependent way (Yamaguchi et al., 2010). In pectoral muscle of chicken, the expression of PGC-1α can promote the formation of type IIb muscle fiber in response to temperature (Ueda et al., 2005). The expression of PGC-1α induced by temperature was different in fish and mammals. The expression of PGC-1α did not changed at 4°C, and was induced at 35°C when goldfish was maintained in the lab at 4, 20 and 35°C for three weeks (LeMoine et al., 2008), while in adult zebra fish, PGC-1α expression was not influenced by temperature (McClelland et al., 2006). The induction of PGC-1α expression by fasting and its effect on muscle fiber type switching was investigated in this study. After two weeks fasting, levels of PGC-1α mRNA were significantly higher in red and white muscle of experimental group compared to control group with approximately3.03 and 4.58-fold (Figure 1).

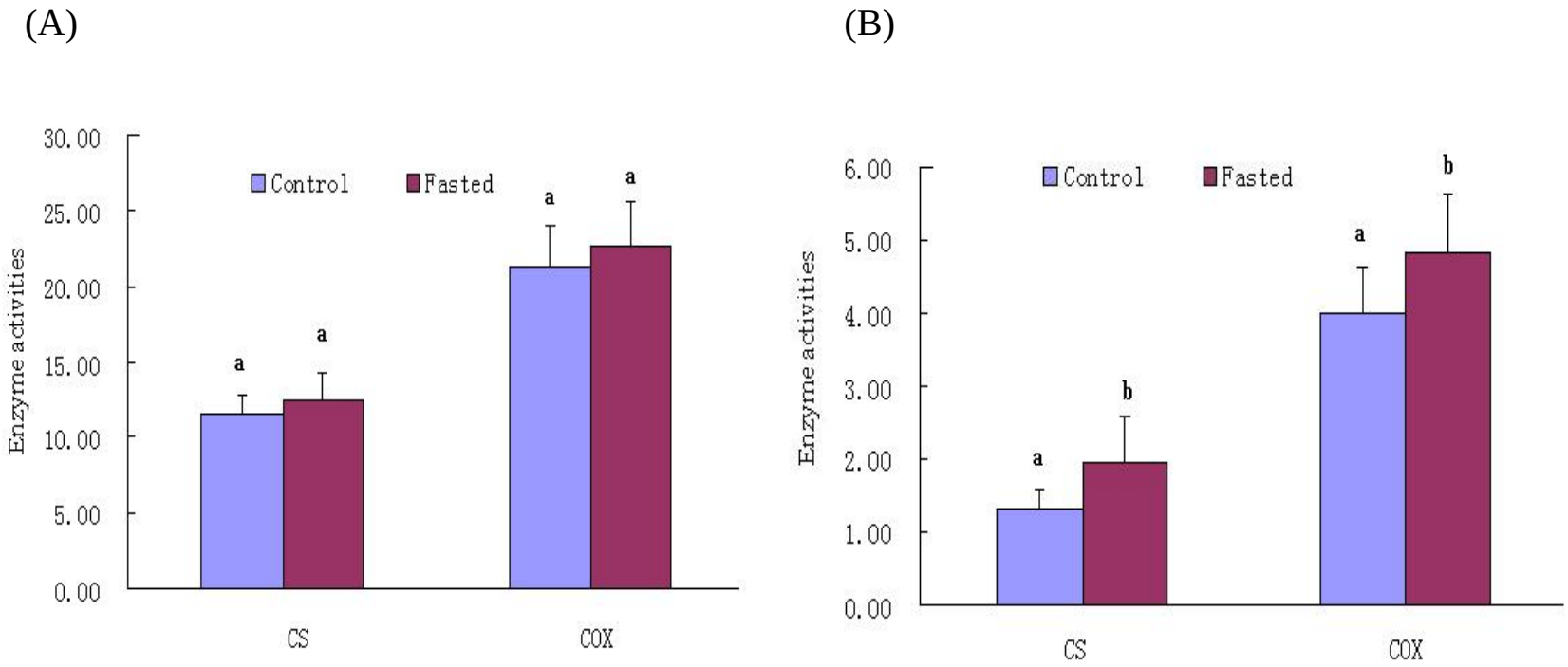

Figure 2. Fasting-induced mitochondria enzyme activities changes in red muscle (A) and white muscle (B) of *S. prenanti*. (A) There was no change in CS and COX in test group; (B) CS and COX were significantly increased than control in white muscle ($P < 0.05$). Data represent the mean values ± SD of eight replicates; values with different letters indicating significant difference ($P < 0.05$).

To further unveil the role of PGC-1α expression on muscle fiber type switching, the expression of mitochondrial-related and fiber-type-related gene and mitochondrial enzymes activity were detected. Both CS and COX enzyme activities (Figure 2) and the level of COX IV mRNA (Figure 3) were significantly higher than control group in white muscle of *S. prenanti* in the condition of fasting, suggesting that PGC-1α was a positive regulator of mitochondrial biogenesis in white muscle. The expression of MyHCI and Mb genes were increased, and the expression of MyHCII was decreased when PGC-1α was induced in white muscle of *S. prenant* (Figure 5). Histological analysis revealed that the characteristics of red muscle fibers also appeared in white muscle after fasting for two weeks (Figure 4). These data indicate that type II fiber displayed characteristics of type I fiber after induction of PGC-1α and which led to switching of II to I fiber-type of *S. prenanti*. Davie et al. (1986) indicated that, muscle oxidative metabolism is increased at same swimming speed for 200 days in *Salvelinus fontinalis*; red fibers mass was increased 2.2 times. Johnston et al. (2000) indicated that, over-nutrition can induce the type I into type II fiber and decrease meat quality of *Atlantic salmon*, but the level of expression of related-gene have not been analyzed. This result suggests that muscle fiber type switching is a complex regulatory system, which can be influenced by outer factors such as environment and nutrition level. While how PGC-1α regulated fiber-type switching is still unclear, it showed that PGC-1α can directly bind unliganded which is involved in hormone receptor families, such as myocyte-specific enhancer factor 2

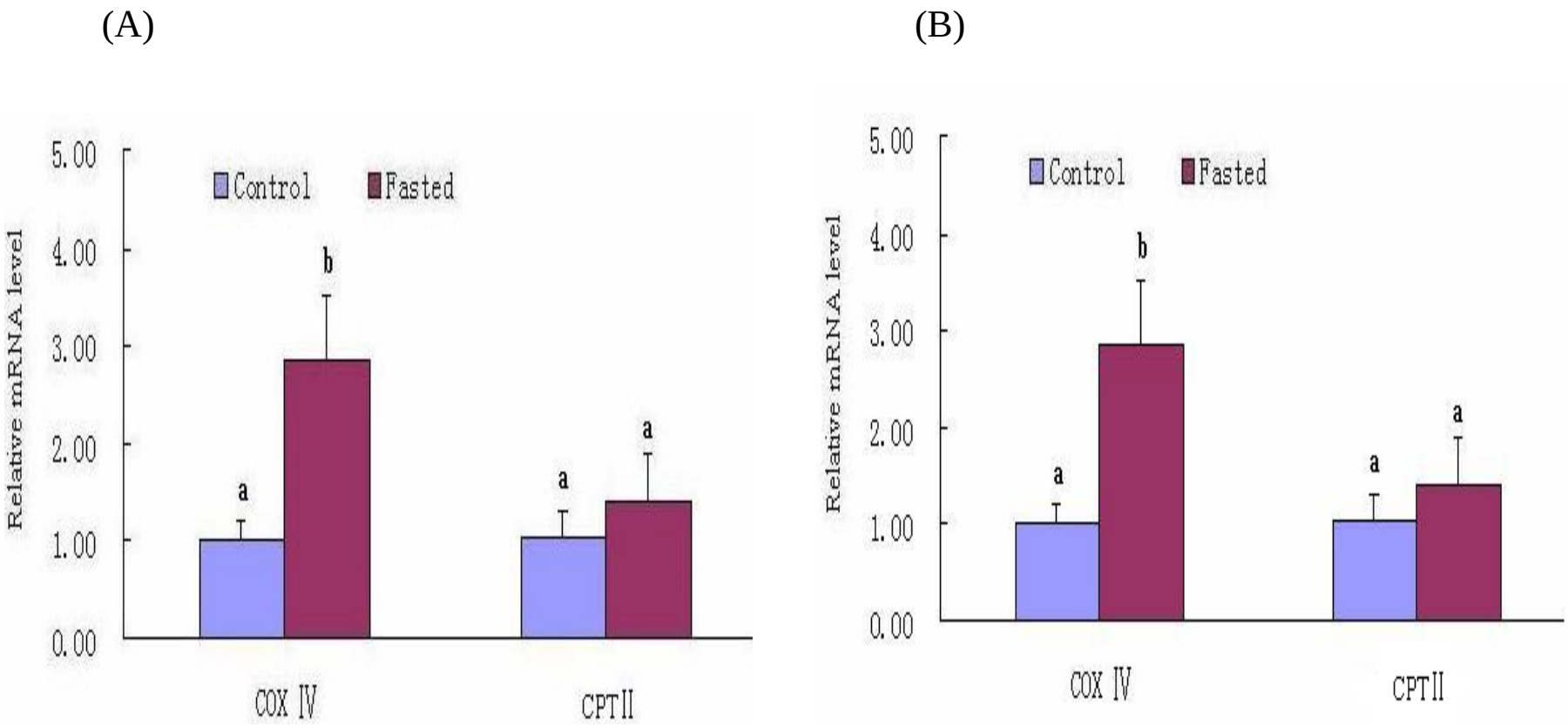

Figure 3. Fasting-induced mitochondria gene mRNA expression changes in red muscle (A) and white muscle (B) of *S. prenanti*. (A) There was no change in COX IV and CPT II mRNA levels in test group. (B) COX IV mRNA level in white muscle was induced, but CPT II did not change significantly with fasting group to control.

(MEF2), peroxisome proliferator-activated (PPAR γ), hypoxia-inducible PGC-1α (HIF-1α), hypoxia-inducible factor-2α (HIF-2α), forkhead box1 (FOXO1) and sirtuin 1 (Sirt1), suggesting that their conformations are conductive to ligand-independent mechanisms of gene regulation.

PGC-1α regulates witching of fiber-type by recruiting MEF2 and HIF-1α (Lin et al., 2002; Rasbach et al., 2010). The purpose of our experiment was to elucidate how PGC-1α regulates switching of fiber-type by alone or synergetic effect.

In conclusion, our results indicate that white muscle fibers also displayed the characteristics of red muscle fibers, and muscle fiber type conversion occurred in *S. prenanti* after two weeks fasting because PGC-1α, after highly expressing by fasting induction regulates the expression of mitochondrial related genes and muscle fiber gene, which plays a pivotal role in the fiber type transformation in *S. prenanti*. *In vivo* experiment of PGC-1α over-expression vector and RNAi vector have been constructed; we are doing transfection of these vectors into myoblast of *S.*

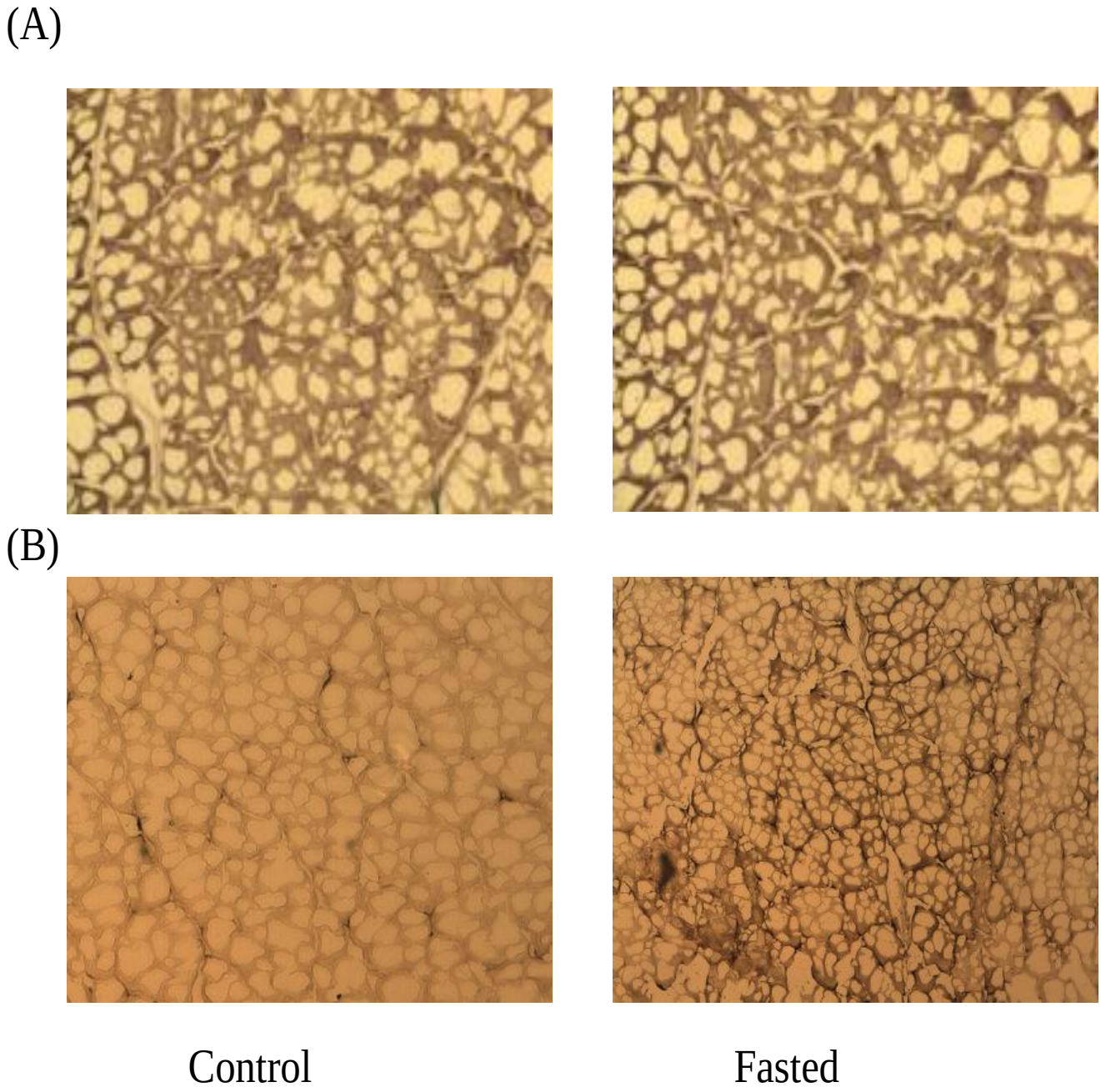

Figure 4. Histological analysis of *S. prenanti* red muscle (A) and white muscle (B). Light microscopy of ATPase (pH 4.3 for type fibers)-stained transverse sections of skeletal muscle specimens from control and fasted *S. prenanti*. Type I muscle fibers were deeply dyed in pre pH 4.3 incubation solutions, while type II muscle fibers were slightly dyed. There was no significant change in the quantities of the type I muscle fibers in fasted group compared to the control, however, there were deeply dyed muscle fibrers in the white muscles of the fasted group, that is the character of the type I muscle fibers.

prenanti to further study the functions and mechanism of PGC-1α in regulating muscle fiber type switching. This study would provide an important theory basis for the fish quality improvement and provide new insights into the mechanism for genetic improvement and breeding work in fish.

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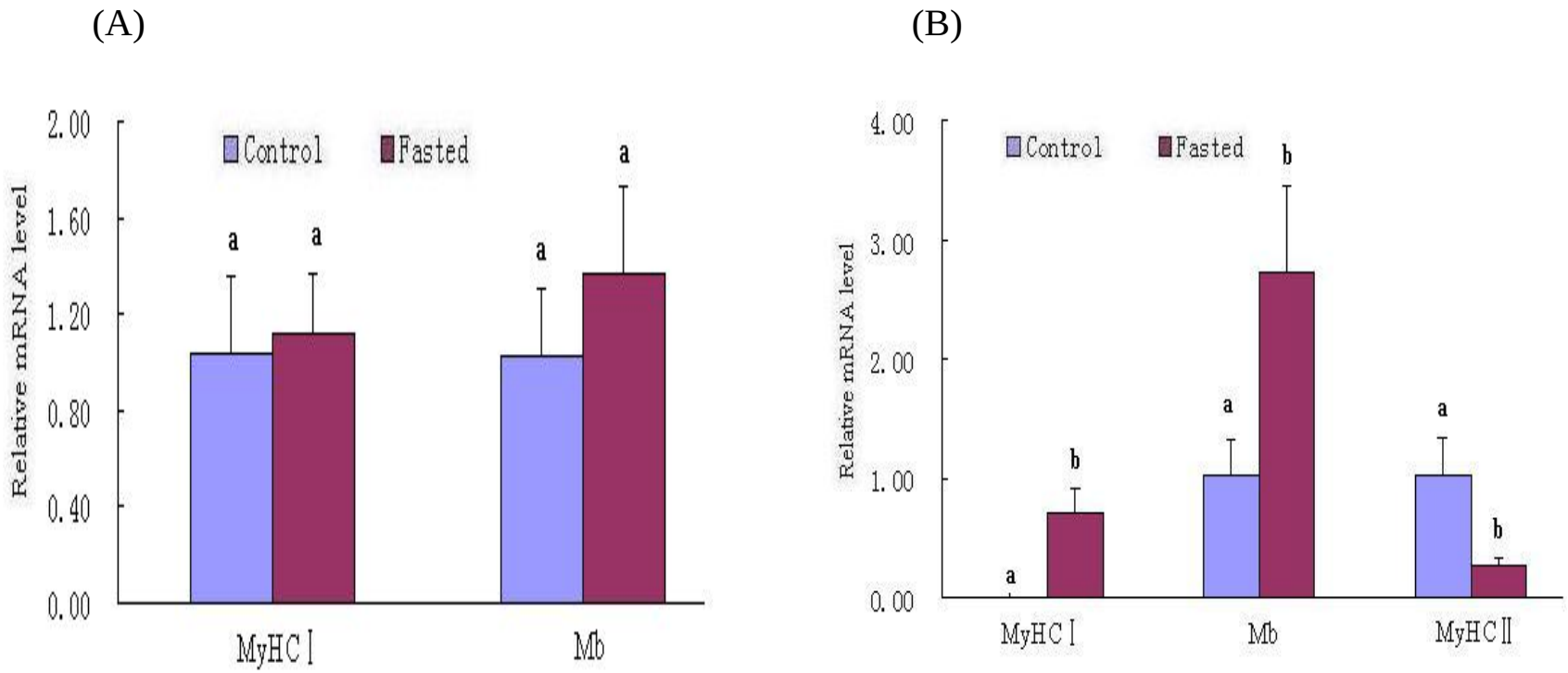

Figure 5. Fasting-induced gene expression changes in red muscle (A) and white muscle (B) of *S. prenanti*. The results indicated that control and fasted group genes had no significant changed in red muscle, but the expresstion of MyHC I (slow) and myoglobin (Mb) were increased in white muscle, MyHC II (fast) expression was significantly decreased ($P < 0.05$).

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