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研究課題名（和文）カルノシンの骨格筋再生における生理的役割の解明、および応用

研究課題名（英文）Roles of carnosine in skeletal muscle regeneration, and its applications

研究代表者
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研究成果の概要（和文）：本研究では、カルノシンが筋衛星細胞（SC）の細胞死感受性を低下させ、SCの増殖を制御することを明らかにした。また、カルノシンが筋再生の初期段階には大きな影響を与えないものの、筋肥大を促進することを見出した。さらに、カルノシン合成の重要な調節因子であるビタミンB6（B6)の欠乏と高容量の摂取の両方が筋再生を遅延させ、筋肥大を抑制することを発見した。しかし、B6の高容量の摂取は、タンパク質分解に関与するMURF-1及びAtrogin-1の発現量を低下させることにより、筋萎縮を抑制することを示した。本研究は、サルコペニア予防におけるカルノシンとB6の新たな役割について貴重な知見を提供するものである。

研究成果の学術的意義や社会的意義
This research is expected to make a significant contribution to society in terms of extending healthy life expectancy by providing the development of nutritional intervention for preventing sarcopenia, which is an extremely important issue for the aging society.

研究成果の概要（英文）：This study demonstrated that carnosine played a role in decreasing susceptibility of satellite cells (SCs) upon activation and in regulating SC proliferation. Carnosine was found to have less effects on the early stage of muscle regeneration, but play a role in maintaining muscle mass and fiber size during muscle growth or hypertrophy. Vitamin B6 (B6) was confirmed to be a carnosine regulator. B6 deficiency was found to markedly decrease carnosine and its substrate β-alanine levels in both mouse skeletal muscles and C2C12 muscle cells. B6 possibly played a role in maintaining quiescent SC pool and supporting proliferation and self-renewal of SCs. Both B6 deficiency and supplementation delayed muscle regeneration and suppressed muscle hypertrophy. However, B6 supplementation suppressed muscle atrophy by down-regulating MURF-1 and Atrogin-1 expressions, protein-degrading genes. The present study provides new insight into novel roles of carnosine and vitamin B6 in preventing sarcopenia.

研究分野：食品科学関連

キーワード：carnosine　muscle regeneration　skeletal muscle　vitamin B6　satellite cells　sarcopenia　muscle atrophy

様　式　C－１９、F－１９－１、Z－１９（共通）

１．研究開始当初の背景

Carnosine (β-alanyl-L-histidine) is an imidazole dipeptide that is highly present in skeletal muscles. Due to its abundance in skeletal muscles, carnosine has been extensively studied for its muscular functions. Although its muscular-protective and exercise-performance enhancement effects have been well reported, its underlying mechanisms remain to be elucidated. In our recent preliminary studies, we have newly found that carnosine may possibly play a role in muscle regeneration process, in which carnosine levels in skeletal muscles were rapidly decreased during the very early stages of muscle injury, 12 h after the injury where muscle-derived amino acid levels still did not change. This preliminary finding suggested that carnosine might degrade itself first, before the occurrence of muscle protein degradation, to contribute to some molecular metabolisms during the acute phase of muscle injury. So far, there are no studies demonstrating effects of carnosine on muscle regeneration and satellite cells (SCs), which are muscle stem cells responsible for muscle regeneration. Thus, in the present study, effects of carnosine on muscle regeneration and SCs will be investigated in the single muscle fiber level. Carnosine-deficient mice will be used to determine effects of endogenous carnosine on both muscle regeneration and SC functions. Moreover, a potent upstream carnosine regulator, vitamin B6, will be investigated for its effects on muscle regeneration and SCs.

２．研究の目的

The main objectives of this study were 1) to determine effects of carnosine on muscle regeneration and SC functions and 2) to determine effects of vitamin B6 on muscle regeneration and SC functions.

３．研究の方法

(1) Animal and diets

Male homozygous *Carns1*$^{-/-}$ mice (13 weeks old) were kindly received from Dr. Ai Egusa of Nippon Veterinary and Life Science University (Tokyo, Japan) and further used for generating *Carns1*$^{-/-}$ and *Carns1*$^{+/-}$ mice used in the present study. For a single myofiber culture experiment to determine effects of exogenous carnosine on SC functions, CD1 mice (male, 8-12 weeks old) were used. For vitamin B6 diet experiments, CD1 mice (male, 5 weeks old) were subjected to a vitamin B6-deficient (1 mg pyridoxine (PN) HCl/kg diet), -supplemented (35 mg PN/kg diet), or -recommended (7 mg PN/kg diet) diet for 8 weeks before further subjected to the single myofiber culture and muscle regeneration experiments. For a muscle atrophy experiment, CD1 mice (male, 5 weeks old) were given vitamin B6-suppremented drinking water (0.0175 g PN/L) for 2 weeks prior dexamethasone administration.

(2) Single myofiber isolation and culture

Extensor digitorum longus (EDL) muscles were harvested and digested using 0.2% w/v collagenase type I (Invitrogen, Carlsbad, CA, USA) by incubating at 37 °C for 2 h. Single myofibers were triturated from the digested muscle bundles and transferred to 10% horse serum-coated cell culture dishes. Then, these isolated single myofibers were either fixed with 4% paraformaldehyde (PFA) immediately (0 h) or cultured at 37 °C for 24, 48, or 72 h, under controlled conditions of 5% CO_2/95% humidified air. The culture medium consisted of high-glucose (4.5 g/L) Dulbecco's modified Eagle's medium (DMEM), 10% horse serum, 0.5% chick embryo extract, and 1% penicillin-streptomycin. For the vitamin B6-deficient culture medium, the vitamin-free DMEM was used. After 24, 48, or 72 h of culture, fixed fibers were co-immunofluorescent stained for Pax7 and MyoD to determine the number and function (self-renewal, proliferation, and differentiation) of SCs remaining on the myofibers. Immunostaining of myofibers freshly isolated (0 h) was used to quantify the number of quiescent SCs.

(3) C2C12 muscle cell culture

The C2C12 cell line (3.0 × 105 cells/well of a 6-well plate) was cultured in a proliferation medium, with or without vitamin B6, at 37 °C under controlled conditions of 5% CO_2/95% humidified air. The proliferation medium was composed of the high-glucose vitamin-free DMEM, 10% fetal bovine serum, 1% penicillin-streptomycin, and vitamins (mg/L at a final concentration), including calcium pantothenate (4.0); choline chloride (4.0); folic acid (4.0); inositol (7.2); niacinamide (4.0); riboflavin (0.4); thiamine HCl (4.0); and PN HCl (4.0). For the vitamin B6-deficient medium, PN HCl was not added. At 80% confluency (after 2 d), the cells were transferred to a differentiation medium, with or without vitamin B6. The differentiation medium was composed of the high-glucose vitamin-free DMEM, 2% horse serum, 1% penicillin-streptomycin, and the abovementioned vitamins. For the vitamin B6-deficient medium, PN HCl was not added. After 4 d of the differentiation, MilliQ water (0.5 mL/well) was added, and the C2C12 cells were collected by scraping for further analysis. Subsequently, the cell extracts were centrifuged at 12,000× g for 10 min at 4 °C. The supernatants were analyzed for the presence of anserine, carnosine, and β-alanine. The protein concentration in each supernatant was determined with a Bio-Rad DC Protein Assay Kit using

bovine serum albumin as the standard.

(4) Carnosine, anserine, and β-alanine analysis

Carnosine, anserine, and β-alanine levels in gastrocnemius (GAS) muscles or C2C12 myotubes were analyzed by ultra-performance liquid chromatography tandem mass spectrometry (UPLCMS/MS; Waters, Milford, MA, USA) equipped with an Acquity UPLC BEH C18 (1.7 μm, 2.1 × 50 mm) column (Waters) and a gradient system with the mobile phase consisting of buffer A (5 mM perfluoroheptanoic acid (PFHpA; SigmaAldrich, Louis, MO) in Milli-Q water) and buffer B (5 mM PFHpA in methanol at a flow rate of 400 μL/min). The details of LC-MS/MS concoctions were described in the paper[1].

(5) Muscle regeneration and hypertrophy

The left leg of tibialis anterior (TA) muscle of each mouse was injected by cardiotoxin (CTX, 10 μM, 100 μL) to induced muscle injury. Then, 5 or 10 days after the CTX-induced injury, TA muscles were harvested and frozen in OCT compound in isopentane cooled by liquid nitrogen for further histochemical and immunofluorescent analyses.

To induce muscle hypertrophy, after the CTX injection, the injured muscles were allowed to growth for 28 days. Then, all mice were subjected to aforementioned CTX injection again. Then, all mice were sacrificed at day 28 after the second CTX injury. TA muscles were harvested and frozen as described above.

(6) Muscle atrophy

To induce muscle atrophy, dexamethasone was used. To establish the dexamethasone administration method, various dexamethasone concentrations and treatment days were investigated. It was found that injection of dexamethasone at 20 mg/kg (i.p.) for 10 days is the best method to induce muscle atrophy in the present study. CD1 mice (male, 5 weeks old) were divided into three groups; a control naïve group, a dexamethasone group, and a dexamethasone + vitamin B6 group. At 2 weeks prior to dexamethasone administration, the control and dexamethasone groups were received drinking water, while the dexamethasone + vitamin B6 group was received vitamin B6-suppremented drinking water (0.0175 g PN/L) until the end of the experiment. After 2 weeks, PBS or dexamethasone was injected daily at 15.00-16.00 for 10 days. Then, TA and GAS muscles were harvested and frozen as described above for histochemical and immunofluorescent analyses. The rest of TA and GAS muscles were used for RNA extraction.

４．研究成果

1) Effects of carnosine on muscle satellite cell functions

We determined if carnosine (exogenous) has any effects on skeletal muscle stem cells, SCs, by applying a single muscle fiber technique. Single fibers were isolated from EDL muscles of CD1 mice and cultured in plating medium containing carnosine at physiological concentrations of 1, 5, or 25mM, for 24 h. As a result, after 24 h of culture, without adding carnosine in the medium, the number of SCs decreased compared to the number of SCs on freshly isolated myofibers (0 h), indicating that SCs possibly underwent cell death after being activated. However, adding carnosine (25 mM) into the cultured medium could prevent such decrease in the number of SCs. When, we extended the culture period to 48 h, we found that the number of $Pax7^{+}/MyoD^{+}$ nuclei, indicating proliferating SCs, of the myofibers cultured in the presence of carnosine was higher than in the control culture. Since the number of SCs significantly decreased after 24 h of activation, we further calculated the proportion of $Pax7^{+}/MyoD^{-}$ (self-renewal), $Pax7^{+}/MyoD^{+}$ (proliferation), and $Pax7^{-}/MyoD^{+}$ (differentiation) nuclei and found no significant difference in the proportion of these nuclei between the two groups. The results suggest that carnosine is unlikely to impact the process of self-renewal, proliferation, and commitment to differentiation. However, it decreases SC susceptibility to early cell death after activation (24 h).

In order to further determine effects of endogenous carnosine on SC functions, myofibers were isolated from EDL muscles of carnosine-deficient mice (homozygous *Carns1*$^{-/-}$) or their control littermates (heterozygous *Carns1*$^{+/-}$ mice), and cultured for 24 h. At the resting stage (0 h, freshly isolated without culturing), *Carns1*$^{-/-}$ mice exhibited the similar number of SCs on myofibers compared to *Carns1*$^{+/-}$ mice, indicating no or less effects of carnosine on quiescent SC pool. However, after 24 h of culture, the number of SCs from *Carns1*$^{-/-}$ mice was significantly decreased, indicating that carnosine is important for preventing SCs from undergoing cell death at the early stages of activation, when SCs are the most vulnerable. To determine the self-renewal, proliferation, and differentiation abilities of SCs, we coimmunostained the 24-h-cultured myofibers for Pax7 and MyoD and found that the *Carns1*$^{-/-}$ myofibers exhibited the significant lower number of $Pax7^{+}$ nuclei, indicating self-renewing SCs, the higher number of $Pax7^{+}/MyoD^{+}$ nuclei, indicating proliferating SCs, and the similar number of $MyoD^{+}$ nuclei, indicating SCs committing to differentiation, compared to the *Carns1*$^{+/-}$ myofibers. The result suggests that carnosine likely to play a role in proliferation of SCs.

2) Effects of carnosine on muscle regeneration and hypertrophy

To determine effects of endogenous carnosine on muscle regeneration, *Carns1*$^{-/-}$ and *Carns1*$^{+/-}$ mice were subjected to a muscle regeneration model. TA muscles of those mice were injured by CTX injection. At 5 days postinjury, there are no significant differences in regenerating muscle mass and myofiber size between *Carns1*$^{-/-}$ and *Carns1*$^{+/-}$ mice. However, when the reinjury model for observing muscle hypertrophy was applied, we found that *Carns1*$^{-/-}$ mice exhibited significant lower regenerating muscle mass and smaller myofiber size than *Carns1*$^{+/-}$ mice. These results suggest that carnosine has less effects on the early stage of muscle regeneration, but possibly plays a crucial role in maintaining muscle mass and fiber size during muscle growth or hypertrophy after muscle regeneration.

3) Effects of vitamin B6 on carnosine synthesis in skeletal muscles

Previously, we found that vitamin B6 is a potent upstream regulator of carnosine in heart muscles[2]. In the present study, we determine if vitamin B6 impacts carnosine synthesis in skeletal muscles. As a result, CD1 mice treated the vitamin B6-deficient diet exhibited a significant decrease in levels of carnosine, anserine, and their substrate β-alanine in GAS muscles, when compared to mice treated a vitamin B6-supplemented diet. To confirm this finding, we determined if vitamin B6 deficiency also suppresses carnosine synthesis in C2C12 muscle cells. We found that in the vitamin B6-deficient medium, the muscle cells exhibited a significant decrease in levels of carnosine and its substrate β-alanine. These results indicate that vitamin B6 is the upstream regulator of carnosine in skeletal muscle. This finding led to the investigation if vitamin B6 also impacts SC functions and muscle regeneration.

4) Effects of vitamin B6 on muscle satellite cell functions

To determine effects of endogenous vitamin B6 on SC functions, single myofibers were isolated from EDL muscles of CD1 mice treated the vitamin B6-deficient and -supplemented diets and subjected to single myofiber culture. At the resting stage (0 h, freshly isolated without culturing), the vitamin B6-deficient myofibers exhibited a significantly lower number of quiescent SCs, as compared to that in the vitamin B6-supplemented myofibers. After 48 and 72 h of culture, the vitamin B6-deficient myofibers exhibited a significantly lower number of proliferating and self-renewing SCs, and the vitamin B6-free medium further decreased this number. These findings indicate that vitamin B6 deficiency induces a decline in the quiescent satellite cell pool and suppresses the proliferation and self-renewal of satellite cells, in which a defect in the proliferation can be reversed by exogenous vitamin B6 addition while a defect in the self-renewal is irreversible. Taken together, it can be hypothesized that a decrease in vitamin B6 itself and vitamin B6-deficient induced carnosine may exert adverse effects on SC viability and functions.

5) Effects of vitamin B6 on muscle regeneration and muscle hypertrophy

Since SC activity directly impacts muscle regeneration, we hypothesized that vitamin B6 status may impact muscle regeneration, in which lower capacity of muscle regeneration and hypertrophy is one of causes leading to sarcopenia. TA muscles of CD1 mice were injured by CTX injection. At 10 days postinjury, mice receiving the vitamin B6-deficient diet exhibited significant lower regenerating muscle mass and smaller myofiber size than mice receiving the vitamin-B6 recommended diet. The result suggest that vitamin B6 deficiency impaired muscle regeneration. Surprisingly, a high dose of vitamin B6 (35 mg/kg diet) worsened muscle regeneration, which was against our expectation.

Next, we determined if vitamin B6 affects muscle hypertrophy by applying a reinjury model, twice CTX-induced muscle injuries with one month recovery after each injury. We found that the vitamin B6 deficient and supplemented diets significantly suppressed muscle hypertrophy. Taken together, these results suggest that both vitamin B6 deficiency and supplementation suppress muscle regeneration and muscle hypertrophy. Further studies are needed to verify the underlying mechanisms and why vitamin B6 supplementation retards muscle regeneration and hypertrophy.

6) Effects of vitamin B6 on muscle atrophy

Since muscle atrophy can lead to the development of sarcopenia, we investigated if vitamin B6 has any effects on muscle atrophy. CD1 mice were divided into three groups, which were a control naïve group, a dexamethasone group, and a dexamethasone + vitamin B6-supplemented group. To induce muscle atrophy, dexamethasone (20 mg/kg BW, ip) was administrated to those mice for 10 consecutive days. As a result, the vitamin B6 supplementation slightly prevented a decrease in muscle weights (EDL, Sol, and GAS). However, the vitamin B6 supplementation could significantly down-regulate expressions of MURF-1 and Atrogin-1, which are muscle or protein degradation genes. These results indicate that vitamin B6 supplementation can prevent muscle atrophy.

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５．主な発表論文等

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掲載論文のDOI（デジタルオブジェクト識別子） 10.3390/nu16010177	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 －

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3．学会等名 2024年度大会（日本農芸化学会創立100周年記念大会）
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〔図書〕　計0件

〔出願〕　計1件

産業財産権の名称 脳内のＧＡＢＡ増加剤	発明者 佐藤三佳子 菅原幸博 矢中規之 カムラン シータナッチャポー	権利者 同左
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〔取得〕　計0件

〔その他〕

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	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関