Chapter

The Effect of Glycation Stress on Skeletal Muscle

Tatsuro Egawa, Kohei Kido, Takumi Yokokawa, Mami Fujibayashi, Katsumasa Goto and Tatsuya Hayashi

Abstract

Glycation stress (glycative stress) is a general concept of biological stress caused by a series of non-enzymatic glycation reactions, including advanced glycation end products (AGEs) formation, AGEs accumulation, glycation-associated dysfunction of proteins and cellular signaling, inflammation, oxidation, and/or tissue damage. There has been increasing evidence supporting a profound effect of AGEs on human diseases such as type 2 diabetes, cardiovascular disease, cancer, Alzheimer's disease, osteoporosis, and dementia, as well as aging process itself. In addition, dietary AGEs intake has also been suggested to contribute to tissue dysfunction and development of the diseases. Skeletal muscle is the largest organ in the human body and important responsibility for maintaining our health as not only locomotor system but also metabolic and endocrine systems. Especially in past decades, numerous studies have suggested the contribution of glycation stress to skeletal muscle dysfunctions (e.g. muscle atrophy, reducing contractile property, and insulin resistance). In this chapter, we provide current evidence on the potential role of glycation stress in the impairment of skeletal muscle functions.

Keywords: glycative stress, skeletal muscle dysfunction, skeletal muscle atrophy, advanced glycation end products, AGEs

1. Introduction

Skeletal muscle is the largest organ in the human body, accounting for approximately 40% of body weight. A primary characteristic of skeletal muscle is its ability to contract and cause movement. In addition, skeletal muscle is a metabolic organ of high metabolic activity regarding nutrient (glucose, lipid, and protein) storage and supply. It has also recently been found that skeletal muscle is a secretary organ that produces and releases cytokines and other peptides, which is known as myokine, that function in manner similar to hormones [1]. Thus, skeletal muscle has an important responsibility for maintaining our health as not only locomotor system but also metabolic and endocrine systems [2]. After the age of 50, approximately 1–2% of muscle mass and 1.5–5% of muscle strength are lost per year [3]. These reductions in muscle mass, strength, and function, the so-called sarcopenia, link to numerous adverse consequences including frailty, disability, morbidity, and mortality [2].

Over the last few decades, there has been increasing evidence supporting a profound effect of advanced glycation end products (AGEs) on human diseases,

including type 2 diabetes, cardiovascular disease, cancer, Alzheimer's disease, osteoporosis, and dementia, as well as the aging process itself [4, 5]. Especially in past decades, many epidemiological studies have suggested the contribution of glycation stress (also called as glycative stress) from AGEs to sarcopenia [6–17]. In this chapter, we provide current evidence on the potential role of glycation stress in the impairment of skeletal muscle functions.

2. Glycation stress

Glycation stress is a general concept of biological stress caused by a series of glycation reactions, including AGEs formation, AGEs accumulation, glycation-associated dysfunction of proteins and cellular signaling, inflammation, oxidation, and/or tissue damage (**Figure 1**).

Protein glycation is a complex series of sequential reactions collectively called the Maillard reaction, which is named after the French chemist Louis Camilli Maillard. The Maillard reaction is divided into three stages, early (the formation of reversible Schiff base and rearrangement to Amadori products), intermediate (the formation of unstable AGEs precursors), and late (the formation of irreversible AGEs products). At the early stage, the carbonyl group of the reducing sugar reacts with the α-amino group at the N-terminal of protein or the ε-amino group of lysine or arginine residue, resulting in a formation of Schiff-base intermediates, followed by a rearrangement to Amadori products, relatively stable ketoamine. Amadori products in the living body include hemoglobin A1c and glycoalbumin. At the intermediate stage, the reaction proceeds and produces highly reactive dicarbonyl intermediates such as 3-deoxyglucosone and methylglyoxal. These intermediates are up to 20,000 times more reactive than glucose in glycation reactions [18]. At the late stage, the intermediates undergo complex reactions such as oxidation, dehydration, condensation, and cleavage to form stable AGEs, with a variety of physicochemical characteristics such as brown color, fluorescence, and cross-linking. Glycation of protein is a post-translational modification that progresses non-enzymatically, unlike enzymatic glycosylation, phosphorylation, acetylation, and glycosylation. Among more than 20 types of AGEs identified in vivo, methylglyoxal-derived hydroimidazolone (MG-H1) and Nε-carboxymethyllysine (CML) are likely the most abundant [19, 20].

Intracellular protein glycation can cause changes in the protein structure due to covalent cross-linking, resulting in the formation of protein misfolding and aggregation [21]. Although these unfunctional proteins are usually degraded through

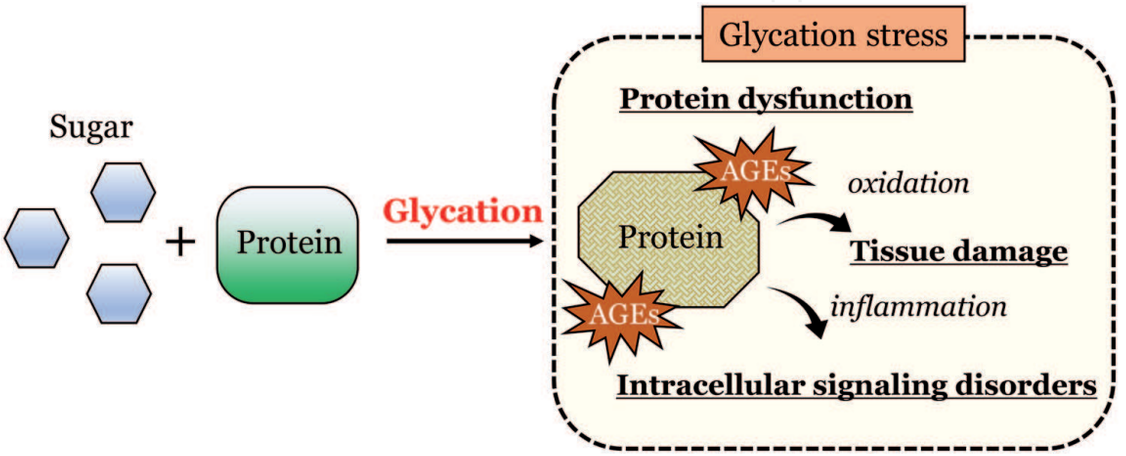

Figure 1.
Conceptual diagram of glycation stress.

ubiquitin-proteasome system, AGEs-modified protein is the lack of free lysine residue needed for ubiquitin conjugation, preventing protein ubiquitination and subsequent its degradation by proteasome [22]. In addition, enzymes present in the ubiquitin-proteasome system and lysosomal proteolytic system are also undergone glycation [23]. Thus, intracellular glycation disrupts proteostasis, inducing cell apoptosis, and thereby increasing the risk of disorders.

On the other hand, extracellular AGEs stimulate several signaling pathways by a series of cell surface receptors. The most studied of which is receptor for AGEs (RAGE), a multi-ligand member of the immunoglobulin superfamily [24]. The activation of AGEs-RAGE axis causes the onset of several diseases, including diabetic complications, cardiovascular disease, Alzheimer's disease, and osteoporosis, by inducing inflammation and the production of reactive oxygen species [25–28]. RAGE is widely expressed in various cells and organs, can be upregulated under pathological conditions where AGEs are increased, and participate in those aging-related pathophysiologies [29]. On the other hand, other groups of cell-surface receptors of AGEs with opposite functions to RAGE, including AGE-R1/Oligosaccharyltransferase 48 KDa Subunit, AGE-R2/protein kinase C substrate 80 K-H, and AGE-R3/galectin-3, and scavenger receptor families act as regulators of endocytosis and clearance of AGEs [30, 31]. These receptors can suppress AGEs-RAGE interaction, but their expressions and functions are impaired during aging and under higher levels of oxidative stress [30]. There is an inverse relationship between AGE-R1 expression and AGEs toxicity [30].

3. Dietary AGEs

AGEs are not only produced endogenously; we ingested them from diet. AGEs content of food depends on the content of protein, fat, and sugar and the types of processing and cooking methods, predominantly on the temperature and duration of preparation [32]. High temperatures during various processes like baking, roasting, frying and grilling promote glycation in food. Scheijen et al. [33] analyzed the content of CML, Nε-carboxyethyllysine (CEL), MG-H1 in the protein fraction of the 190 food items by UPLC-MS/MS, and they showed that CML and CEL were contained in <7 mg/100 g in high-content foods such as fried bacon, chocolate, and peanut butter. The content of MG-H1 was higher compared to those of CML and CEL, and it was <65 mg/100 g in high-content foods such as black pudding, peanut butter, cereals, and biscuit.

Proteins are digested into amino acids and small peptide in the gastrointestinal tract. Therefore, dietary AGEs are expected to be absorbed in the circulation mostly in the form of free AGEs and AGEs-modified peptides. The amount of AGEs absorbed in the circulation was estimated to be 10% in healthy people; 1/3 of the absorbed AGEs are excreted in urine within 48 hours and 2/3 remained in the body [34]. For healthy people, a daily AGEs intake of around 9,000–23,000 kU/day was determined [32]; one AGE Unit was defined as the amount of antibody-reactive material that was equivalent to that in 1 μg of an AGEs-BSA standard. The AGEs content of major meals [35] is listed in **Table 1**.

A cross-sectional study revealed that higher levels of dietary AGEs were associated with higher levels of free plasma and urinary AGEs [36]. In addition, a tracer study using $^{13}C_2$-CML found that dietary CML was accumulated in kidney, ileum, colon, lung, brain, testis, heart muscle, skeletal muscle, and liver, but not in fat [37], suggesting the contribution of dietary AGEs to tissue dysfunction and development of diseases. In fact, a meta-analysis of 13 randomized controlled trials showed a decrease in metabolic parameters including body weight, insulin resistance, total

Meal	AGEs kU/serving	Calory kcal/serving
Carbonara spaghetti (280 g)	27,033	1,043
Sirloin steak (200 g)	26,843	1,003
Mixed pizza (1/2 piece)	21,783	1,211
Seafood pizza (1/2 piece)	19,676	1,211
Beef cutlet curry (450 g)	17,337	1,407
Hamburger steak (220 g)	11,170	453
Roasted dumplings (10 pieces)	8,668	627
Fried chicken (130 g)	7,997	532
Fried shrimp (245 g)	7,290	588
Deep-fried tofu (155 g)	6,063	204
Salt-grilled saury (130 g)	6,032	315
Hamburger (1 piece)	5,851	302
Soy sauce ramen (270 g)	5,377	476
Fried egg (2 pieces)	4,304	257
Fried potato (160 g)	4,099	448
Cream puff (1 piece)	3,799	123
Fried noodles (190 g)	3,628	512
Strawberry sponge cake (1 cut)	2,998	539
Toast with butter (1 piece)	2,447	259
Spaghetti with meat sauce (280 g)	2,063	616
Tofu with soy sauce (118 g)	624	73
Boiled egg (2 pieces)	382	211
Potato salad (140 g)	249	372
Miso soup (1 cup)	227	39
Raw egg (2 pieces)	164	211
Udon noodles (130 g)	71	339
Strawberry (120 g)	52	96
Banana (90 g)	51	78
Boiled spinach (30 g)	30	9
White rice (150 g)	16	252

Table 1.
AGEs content in meals.

cholesterol, low-density lipoprotein, and leptin and an increase in adiponectin levels after consumption of low AGEs diets compared to high AGEs diets [38, 39]. This study indicates that the restriction of AGEs from food can be effective in reducing the incidence of chronic metabolic diseases and promoting health.

4. The effect of AGEs on skeletal muscle

4.1 AGEs accumulation and skeletal muscle dysfunction

In this about 10 years, epidemiological studies have reported the relationship between AGEs level in the body and skeletal muscle functions. The first report by

Dalal et al. [6] found an association between elevated serum CML level and poor grip strength in 559 older women with physical disability (≥ 65 years old). A similar result was observed in the InCHIANTI study, which is a population-based prospective cohort study conducted in the Chianti region in Italy. The study showed that elevated plasma CML level was at high risk of slow walking speed (odds ratio 1.56, 95% confidence interval 1.02–2.38, P = 0.04) in 944 older community-dwelling adults (≥ 65 years old) [7]. Sun et al. [9] also reported that elevated serum CML level was a risk factor for developing severe walking disability. In the study, which had a 30-month follow-up in 394 older women (≥ 65 years old), it was shown that compared with the group of lower three quartiles of CML, the patients in the group of highest quartile of CML were more likely to develop severe walking disability (hazard ratio 1.54, 95% confidence interval 1.04–2.29, P = 0.03). A community-based cross-sectional study by Yang et al. [16] showed that urinary CML level was negatively associated with grip strength among 41 older women but not 63 older men (≥ 65 years old). Furthermore, the joint association of urinary CML level and mobility function was correlated with the risk of developing sarcopenia among older adults (odds ratio 13.76, 95% confidence interval 1.03–183.83, P < 0.05). In addition to CML, increased serum pentosidine, a well-known AGEs found in the plasma and tissues of diabetic and uremic subjects [40], was shown to be negatively associated with skeletal muscle mass in 133 postmenopausal women with type 2 diabetes (mean age 66.8 years) [10] and in 70 elderly women with or without sarcopenia (≥ 53 years old) [17].

These findings are also supported by studies using non-invasive AGEs measurement methods. Because several AGEs have characteristic fluorescence, the measurement of skin autofluorescence (SAF) is often adopted to assess the level of AGEs in the body. Momma et al. [8] investigated the relationship between SAF and muscle strength and power in 232 adult men (median age 46.0 years) and found that participants with higher SAF had lower grip strength and leg extension power. Kato et al. [11] also reported that SAF was significantly higher in the low skeletal muscle index group compared with the normal skeletal muscle index group among 132 elderly people (mean age 59.0 years). Moreover, SAF was shown to be an independent factor associated with low skeletal muscle index (odds ratio 15.7, 95% confidence interval 1.85–133.01, P = 0.012). The negative association between SAF and muscle mass (odds ratio 1.48, 95% confidence interval 1.23–1.78, P < 0.001), grip strength (odds ratio 1.98, P = 0.003), hip flexion strength (odds ratio 1.50, P = 0.012), and hip abduction strength (odds ratio 1.78, P = 0.001) was found among 9,203 participants (mean age 57.8 years) in the Nagahama study, which is a large-scale population-based cohort study in Japan [13]. Another large population-based cohort study in the Netherlands, the Lifelines study also demonstrated the relationship between SAF and poor physical functioning among 5,624 participants (≥ 65 years old) [14]. In a study of diabetic patients, Mori et al. [12] reported that knee extension power was negatively correlated with SAF among 36 patients with type 1 diabetes (mean age 55.7 years). They subsequently reported that SAF was the independent determinant for skeletal muscle mass index (odds ratio 6.38, 95% confidence interval 1.93–21.08, P < 0.05), grip strength (odds ratio 3.55, 95% confidence interval 1.57–8.00, P < 0.05), knee extension power (odds ratio 3.68, 95% confidence interval 1.87–7.23, P < 0.05), and sarcopenia (odds ratio 7.73, 95% confidence interval 2.13–28.02, P < 0.05) among 166 patients with type 2 diabetes (mean age 63.2 years) [15]. Collectively, accumulation of AGEs may be a better predictor of skeletal muscle dysfunctions during aging process. Furthermore, recent our preliminary study found that SAF was negatively associated with leg extension power in 20 health young men (mean age 19.0 years) (**Figure 2**). Therefore, glycation stress may affect muscle strength even in young people, and it is considered

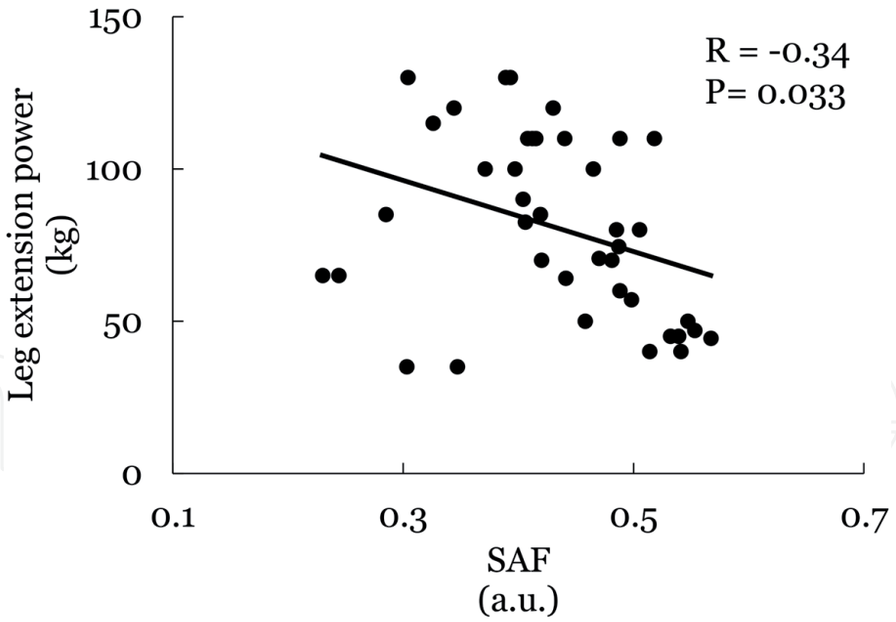

Figure 2.
Correlation between skin autofluorescence (SAF) and leg extension power. The subjects were 20 healthy young men, and after measuring the subcutaneous glycation state with an AGEs sensor (RQ-AG01J, Sharp Life Sciences, Hyogo, Japan), the maximum lift weight of leg extension was measured. Statistical significance was assessed using Pearson's correlation.

that grasping the glycation stress state not only from the elderly but also from the young age can contribute to the prevention of future muscle dysfunctions.

4.2 AGEs modification of contractile proteins in skeletal muscle

Decreased skeletal muscle quantity is deemed a crucial cause of aging-associated muscle dysfunctions. However, recent evidence suggests that the quality of muscle tissue is more functionally relevant than its quantity. Muscle contractile properties are identified as an important determinant of functional limitations in older adults [41]. In this context, several studies have focused on the effect of intracellular glycation on protein structure and function in skeletal muscle. Syrovy and Hodny [42] first reported in 1993 that incubation of myofibrils with ribose promoted the glycation of myofibrillar proteins such as myosin heavy chain, α-actinin, actin, and tropomyosin, accompanied by reduced ATPase activity. The decrease in ATPase activity associated with the glycation is supported by several subsequent studies [43–45]. A major component of skeletal muscle, myosin contains 201 lysine residues and offers numerous potential sites for glycation. In fact, Ramamurthy et al. [46] demonstrated that glucose exposure to rodent skeletal muscle fiber induced myosin structural change and reduction of shortening velocity of myosin. The study is the first report to show the glycation-induced protein structural and functional changes in skeletal muscle. Furthermore, some researchers have found that actin and connective tissues were also modified with AGEs in skeletal muscle of old rats [47] and human [48]. Structural or chemical changes in actin, myosin, and extracellular matrix are likely to deteriorate muscle function by affecting actomyosin ATPase activity or stiffness [49, 50]. Our preliminary experiment also found that 45 AGEs-modified proteins were increased in skeletal muscle of old mice (24-month age) compared with that of young adult mice (6-month age) (unpublished data). These intracellular or extracellular AGEs modifications of skeletal muscle proteins may be a potent factor of aging-associated skeletal muscle dysfunctions.

4.3 AGEs and insulin resistance in skeletal muscle

In skeletal muscle, the initial insulin signaling events include insulin binding to the extracellular α-subunit of the insulin receptor, rapid phosphorylation of the receptor (auto-phosphorylation) and insulin receptor substrate (IRS)-1 on tyrosine residues, and recruitment and activation of class IA phosphatidylinositol 3-kinase. These lead to the generation of the critical second messenger PI-3,4,5-triphosphate, which in turn triggers the activation of Akt [51]. TBC1 domain (TBC1D) family member 1 and TBC1D4 act as downstream mediators of Akt. TBC1D1 and TBC1D4 contain a Rab-GTPase-activating protein domain that prevents glucose transporter 4 (GLUT4) translocation by inactivating Rab proteins. TBC1D1 and TBC1D4 dissociate from GLUT4 vesicles in the phosphorylated state, and thereby facilitating GLUT4 translocation and glucose transport [52, 53].

Many evidence have shown that AGEs impair insulin signaling transduction and induce insulin resistance in skeletal muscle. Miele et al. [54] showed that exposure of glycated albumin (0.1–0.2 mg/ml) to skeletal muscle cells for 24 hours impaired insulin-stimulated 2-deoxyglucose uptake, accompanied by reduced IRS-1 tyrosine phosphorylation, Akt activity, but not insulin receptor kinase activity, suggesting that AGEs affect factors downstream from insulin receptor. AGEs-induced inhibition of glucose transport was supported by the work of Wu et al. [55] that exposure of glyoxal-derived AGEs (0.1 mg/ml) to skeletal muscle cells for 8–48 hours completely abolished 2-deoxyglucose uptake. Their subsequent research found that AGEs-induced impairment of insulin action might be mediated by the formation of multimolecular complex among RAGE/IRS-1/src and protein kinase C [56]. Animal study by Rai et al. [57] demonstrated that fructose intake (20% in drinking water) for 16 weeks decreased insulin-stimulated Akt phosphorylation accompanied by elevated serum and muscle AGEs level and RAGE mRNA level in rat skeletal muscle. However, these changes were suppressed by co-ingestion of AGEs inhibitor aminoguanidine (100 mg/kg). Pinto-Junior et al. [58] showed that injection of glycolaldehyde-derived AGEs (20 mg/kg/day) to rat for 12 weeks led to whole-body insulin resistance and decreased GLUT4 mRNA and protein levels in skeletal muscle. Furthermore, they demonstrated that exposure of glycolaldehyde-derived AGEs (1.0 mg/ml) to skeletal muscle cells for 2.5 hours increased nuclear factor (NF)-κB expression and nuclear protein binding activity into a GLUT4 gene promoter NF-κB binding site, suggesting that AGEs reduce GLUT4 transcription through NF-κB signaling. These AGEs-induced aggravating effect on insulin signaling may induce skeletal muscle insulin resistance, and thereby contributing to impairment of whole-body glucose homeostasis with aging or diabetes.

4.4 The effect of AGEs on myogenesis, development, atrophy of skeletal muscle

As described above, AGEs are a crucial factor affecting skeletal muscle functions, especially skeletal muscle mass. Considering the formation process of AGEs derived from sugar, it has been initially investigated the effects of AGEs on diabetic muscle atrophy. Snow et al. [59] observed distribution patterns of AGEs in skeletal muscle of diabetic rats and found the presence of CML intracellularly and at sites along the muscle fiber periphery. However, there was no difference in muscle fiber cross-sectional area between AGEs-positive and -negative fibers in both control and diabetic rats, indicating the indirect effect of intracellular AGEs on muscle size. Alternatively, a more detailed study by Chiu et al. [60] demonstrated that decreased muscle mass and fiber cross-sectional area in diabetic rats was attenuated by the 4-week treatment with AGEs inhibitor, alagebrium chloride, accompanied by

decreased AGEs and RAGE expressions. They also investigated the direct effect of AGEs on muscle atrophy and found that exposure of glucose-derived AGEs (0.025–0.2 mg/ml) to human primary skeletal muscle cells for 48 hours induced myotube atrophy via RAGE, 5'AMP-activated protein kinase, and Akt signaling-mediated upregulation of ubiquitin-proteasome system.

Our recent study supports the involvement of RAGE in skeletal muscle atrophy. In addition to diabetes, muscle disuse due to injury, casting, and bedrest is a potent inducer of muscle mass loss [61]. However, there was no evidence that glycation stress was involved in disuse-induced skeletal muscle atrophy. Therefore, we investigated the contribution of RAGE to disuse-induced skeletal muscle atrophy [62]. Our study showed that 1-week hindlimb suspension procedure to mice led to muscle atrophy accompanied by intracellular MG-H1 and CML accumulations. However, treatment with RAGE antagonist during the suspension attenuated the atrophic response (**Figure 3**), and muscle mass inversely correlated with the accumulation of MG-H1 and CML in skeletal muscle (**Figure 4**). RAGE inhibition also suppressed the atrophy-associated expression of proinflammatory cytokines and activation of ubiquitin-proteasome system. These findings suggest the contribution of RAGE to

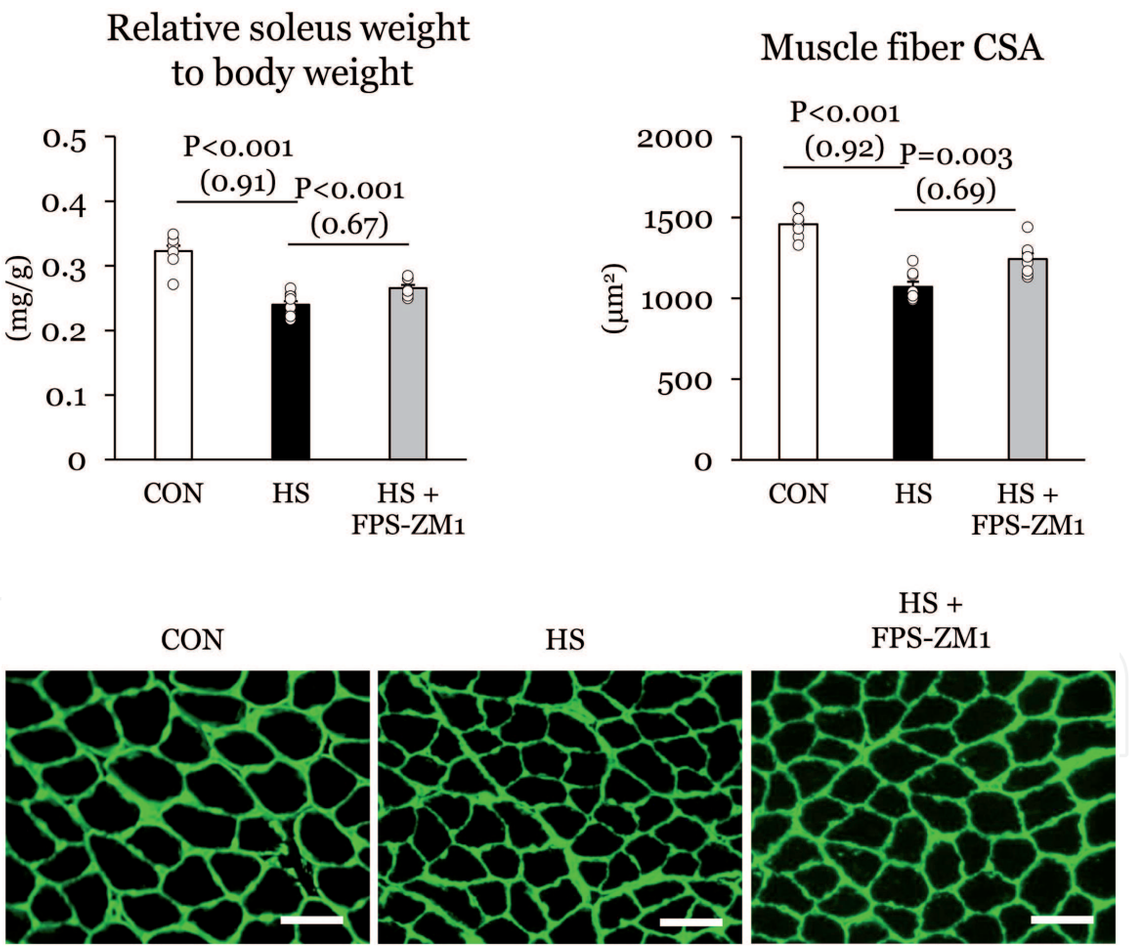

Figure 3.
Soleus weight normalized to body weight and muscle fiber cross sectional area (CSA) after hindlimb suspension and/or receptor for AGEs (RAGE) antagonist treatment. Mice in the HS group were subjected to continuous hindlimb suspension for 1 week. Age-matched mice that did not undergo hindlimb suspension were used as controls (CON). Mice in the HS + FPS-ZM1 group were injected daily intraperitoneally with 1 mg/kg FPS-ZM1, a RAGE antagonist, during hindlimb suspension. Data are expressed as means ± SE; n = 7–9 per group. Individual data points are indicated on the bar graph. Representative images of immunofluorescence are shown. Scale bars, 50 μm. The value of effect size is listed in parentheses. Statistical significance was analyzed using Tukey–Kramer multiple comparison tests. This figure was adapted from Egawa et al. [62] with permission from the publisher.

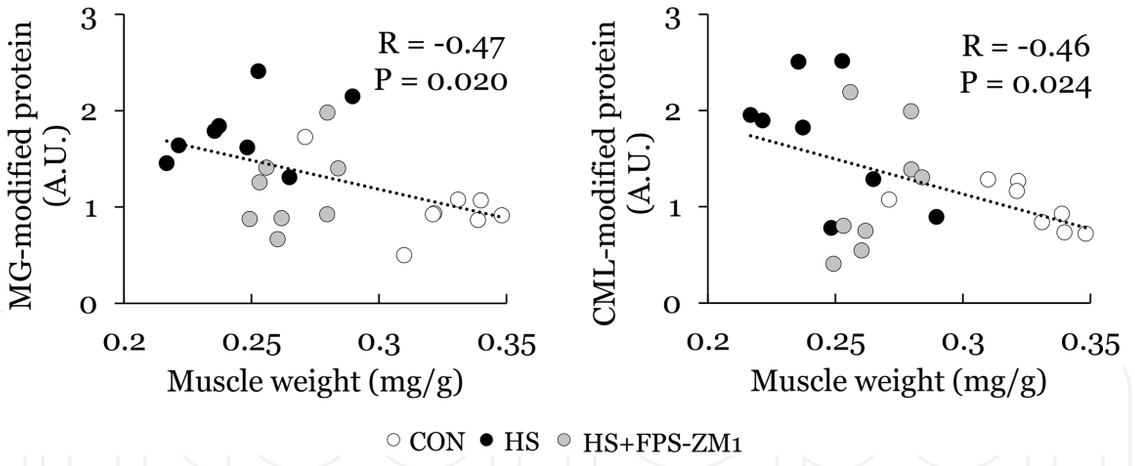

Figure 4.
The correlation between methylglyoxal (MG)- or Nε-(carboxymethyl) lysine (CML)-modified protein level and muscle weight. For the quantification of MG-modified and CML-modified proteins, the signal intensity of full-molecular-weight was quantified after western blotting. n = 8 per group. Statistical significance was assessed using Pearson's correlation. This figure was adapted from Egawa et al. [62] with permission from the publisher.

disuse-induced skeletal muscle atrophy. Furthermore, in this study, RAGE expression was increased in response to suspension, and this was limited to atrophied soleus and plantaris muscles but not unatrophied extensor digitorum longus muscle. Therefore, muscle disuse itself but not systemic mediators may regulate RAGE expression.

The effect of glycation stress on muscle growth was first reported in our research [63]. We evaluated the differences in muscle mass, contractile properties and molecular responses between mice that received a diet containing high-AGEs and low-AGEs for 16 weeks [63]. As a result, exposure to a high-AGEs promoted CML accumulation in skeletal muscle, suppressed muscle growth, and induced skeletal muscle dysfunctions including suppression of muscle strength, fatigue resistance, and force production (**Figure 5**). In addition, the expression of myogenic factors and phosphorylation of p70 s6 kinase, an enzyme playing a key role in the regulation of protein synthesis, were decreased in the high-AGEs treated group. These results suggest that exposure to AGEs impairs postnatal growth and muscle development.

To clarify the underlying mechanism of AGEs-induced inhibition of muscle growth, we next carried out the comprehensive analysis of protein phosphorylation status by using the reverse phase protein array method [64]. In the study, the average level of phosphorylation of skeletal muscle cells exposed to various kinds of AGEs (glyoxylic-, pyruvate, glycolaldehyde, and glucose-derived AGEs, 0.1 mg/ml) was increased at eight phosphorylation sites and decreased at 64. The most upregulated phosphorylation sites were signal transducer and activator of transcription 3 (STAT3) Tyr^{705}. The most downregulated phosphorylation sites were extracellular signal-regulated kinase (ERK) Thr^{202}/Tyr^{204}. Almost all of the phosphorylation sites related to insulin/insulin-like growth factor 1 (IGF-1) signaling were also downregulated by AGEs (**Figure 6**). Increased STAT3 Tyr^{705} phosphorylation and decreased ERK Thr^{202}/Tyr^{204} phosphorylation were also confirmed in the skeletal muscles of mice treated with a diet high in AGEs for 16 weeks. These results suggest that systemic AGEs modulate cellular signaling transduction pathways, such as STAT3 and insulin/IGF-1 signaling, and thereby contribute to the impairment of skeletal muscle growth and development. Accordingly, Adachi et al. demonstrated that IGF-1 treatment protected AGEs-induced deterioration of myogenic differentiation in skeletal muscle cells [65].

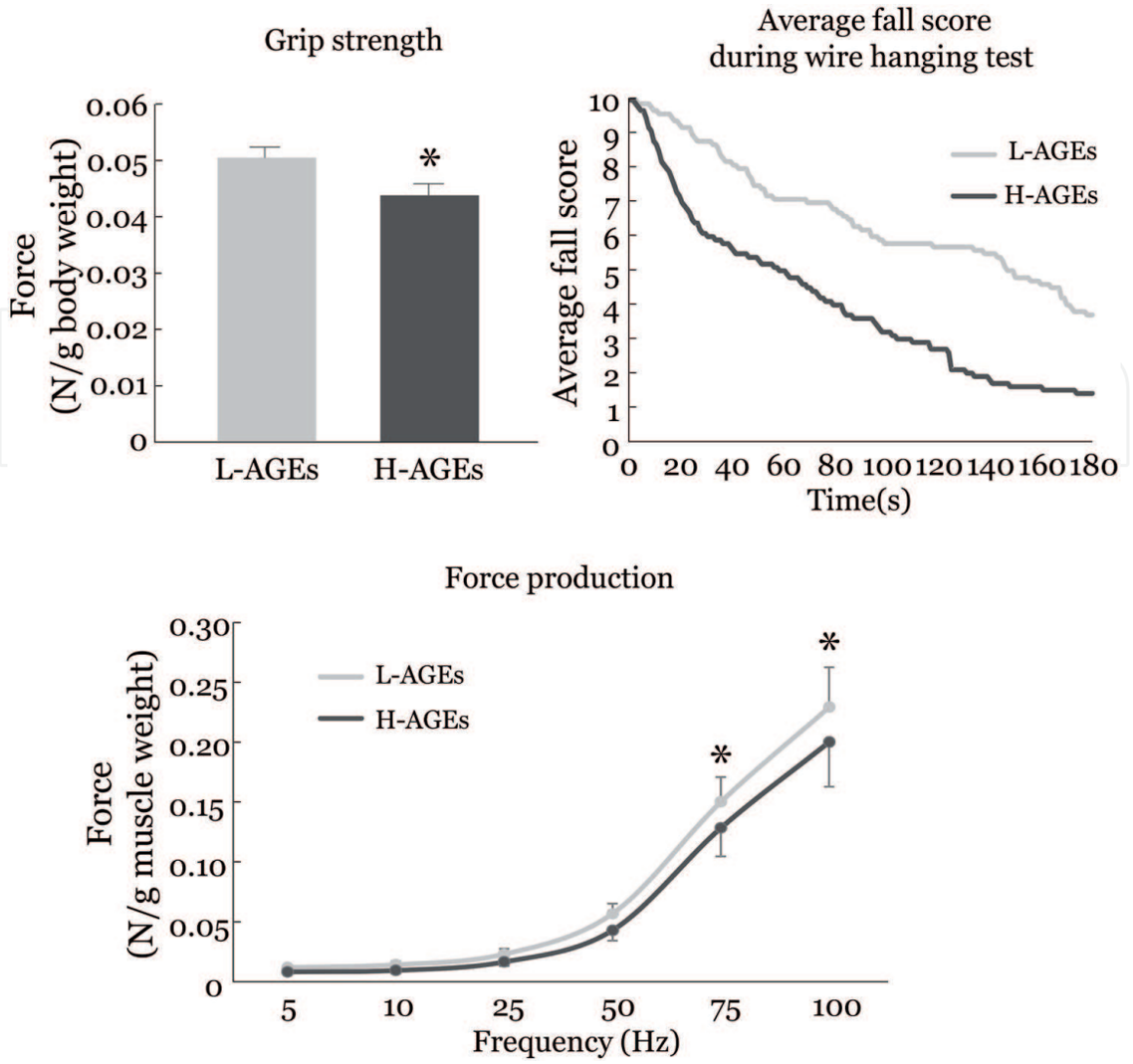

Figure 5.
*The grip strength test, wire-hanging test, and in vitro force production of plantaris muscles in mice fed a diet low in AGEs (L-AGEs) or a diet high in AGEs (H-AGEs). The grip strength test and wire-hanging test was conducted 5 and 4 days before the end of the 16-week study, respectively. For measuring in vitro forth production, isolated plantaris muscle was allowed to rest for 30 min and the muscle was tetanically contracted at frequencies of 0, 5, 10, 25, 50, 75, and 100 Hz with a 2 min rest between contractions. Data are expressed as mean ± SE, n = 10 per group. *P < 0.05 vs. L-AGEs mice. Statistical significance was analyzed using Student's t test or Tukey–Kramer multiple comparisons tests. This figure was adapted from Egawa et al. [63] with permission from the publisher.*

5. Therapeutic perspectives for AGEs-induced skeletal muscle dysfunctions

AGEs-RAGE axis seems to be the most contributor to skeletal muscle dysfunctions under glycation stress condition [66]. Recently, Chiappalupi et al. [67] demonstrated that cancer cachexia-induced muscle wasting and inflammatory responses were prevented in RAGE-null mice. In this regard, several RAGE antagonists were used for preclinical and clinical studies [68, 69]. For example, FPS-ZM1, which was identified by screening 5,000 compounds for their ability to inhibit RAGE and amyloid-β interaction, can block amyloid-β-induced cellular stress [70]. Azeliragon, which is an orally-active small-molecule antagonist of RAGE, improves cognitive function in Alzheimer disease patients by inhibiting inflammation and amyloid-β accumulation [71]. As our study showed, RAGE inhibition by FPS-ZM1 could prevent disuse-induced muscle atrophy [62]. Potentially, these RAGE inhibitors might be useful for various skeletal muscle atrophy.

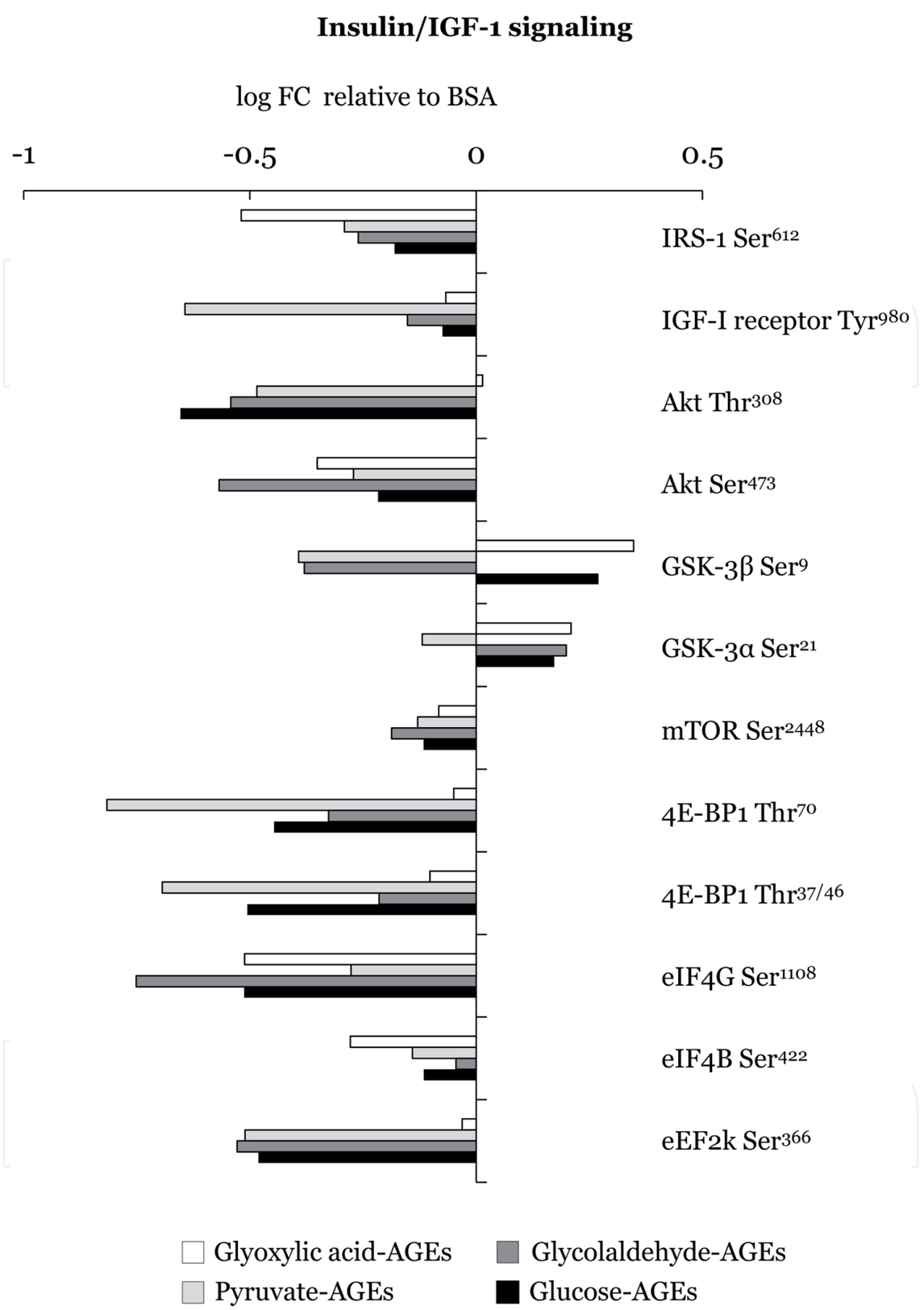

Figure 6.
The phosphoproteins related to insulin/insulin-like growth factor-1 (IGF-1) signaling. C2C12 myotubes on day 4 of differentiation were incubated with glyoxylic acid-derived AGEs, pyruvate- derived AGEs, glycolaldehyde- derived AGEs, glucose- derived AGEs, or BSA at 0.1 mg/mL for 24 h. After that, reverse phase protein array analysis was performed. The phosphoproteins related to insulin/IGF-1 signaling are represented as the relative log fold-change (FC) values. This figure was adapted from Egawa et al. [64] with permission from the publisher. IRS-1, insulin receptor substrate-1; IGF-1, insulin-like growth factor-1; GSK, glycogen synthase kinase; mTOR, mammalian target of rapamycin; 4E-BP1, eukaryotic translation initiation factor 4E binding protein- 1; eIF, eukaryotic translation initiation factor; eEF2k, eukaryotic elongation factor- 2 kinase.

Plant-derived phytochemicals are also potentially beneficial for maintaining muscle functions. Screening of 536 kinds of plants has confirmed anti-glycation activity in more than 100 kinds of materials [72]. Recent our study [73] found that propolis, a natural resinous substance produced by honeybees, has an inhibitory effect on AGEs formation. Furthermore, propolis intake (0.1%-containing diet) for 20 weeks under glycation stress conditions from methylglyoxal exposure prevented intracellular MG-H1 accumulation and inflammatory cytokine expressions in mouse skeletal muscle (**Figure 7**).

In addition to phytochemicals, organic compound with anti-glycation effect, pyridoxamine has been shown to inhibit diabetes-related muscle dysfunctions. Muellenbach et al. [74] first showed that treatment with pyridoxamine (60 mg/kg i.p. injection) for 6 weeks improved insulin-stimulated glucose transport in the skeletal muscle of obese Zucker rats. In a study by Hagiwara et al. [75] using a high-fat diet fed rats, it was shown that 12-week treatment with pyridoxamine (300 mg/kg/day in drinking water) attenuated reductions in Akt phosphorylation and GLUT4 expression in the plasma membrane of skeletal muscle. Mastrocola et al. [76] demonstrated that pyridoxamine treatment to rats fed a high-fructose diet (60% of calories) for 12 weeks suppressed CML accumulation, RAGE upregulation, sirtuin-1 reduction, mitochondrial dysfunction, and contractile dysfunction in skeletal muscle. These

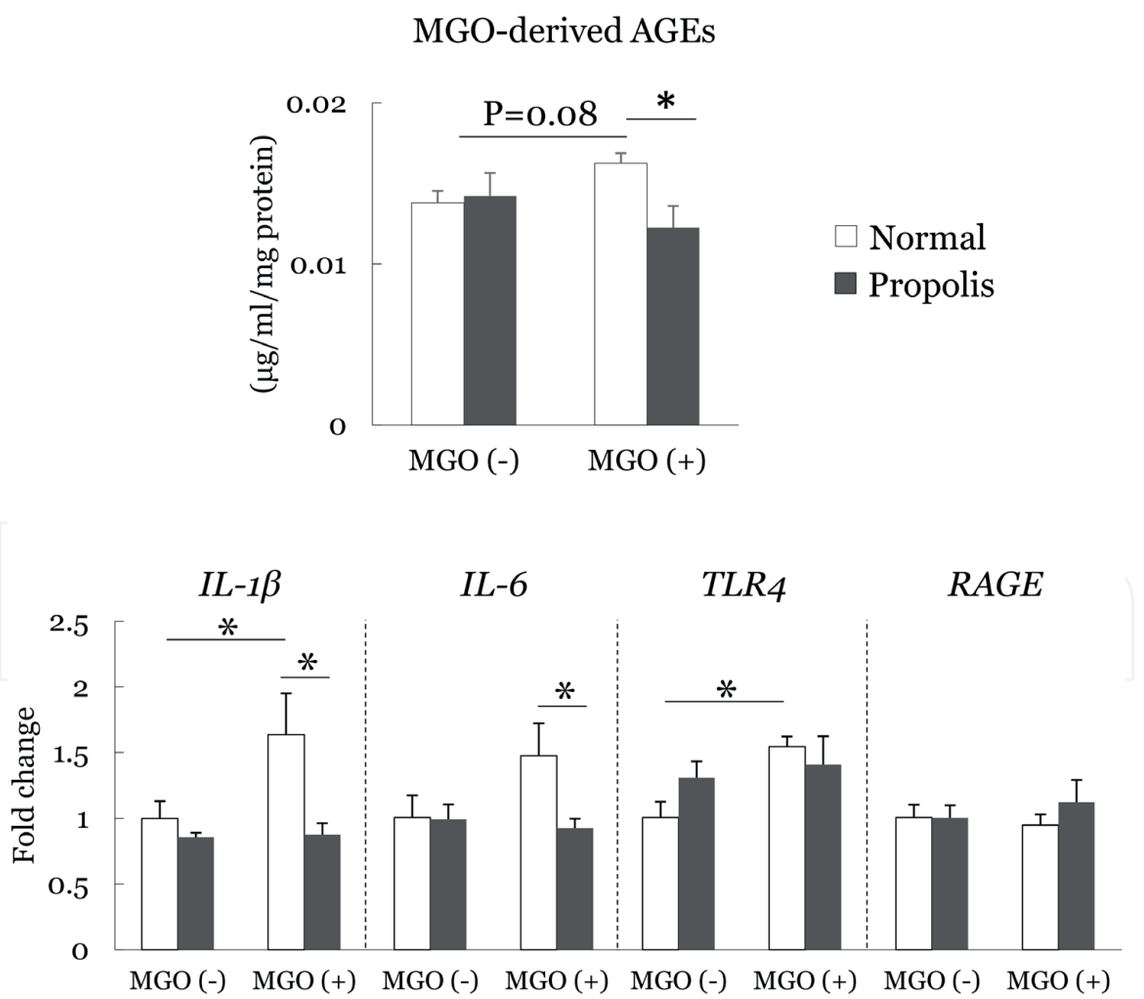

Figure 7.
*The content of methylglyoxal (MGO)-derived AGEs and mRNA expression of interleukin (IL)-1β, IL-6, toll-like receptor 4 (TLR4), and receptor for AGEs (RAGE) in the extensor digitorum longus muscles. The muscles were dissected from mice treated with or without propolis (0.1%)-containing diet or MGO (0.1%)-containing drinking water for 20 weeks. Data are expressed as means ± SE; n = 3–6 per group. * P < 0.05 between the groups. Statistical significance was analyzed using Tukey–Kramer multiple comparisons tests. This figure was adapted from Egawa et al. [73] with permission from the publisher.*

results suggest that even in situations where glycation stress increase such as high-AGEs diet intake, skeletal muscle dysfunctions can be prevented by simultaneously ingesting compounds and foods that have anti-glycation effects.

6. Conclusion

Glycation stress is a potential factor that reduces physical functions, which has become attention in recent years as well as oxidative stress. Glycation stress is mainly caused by intracellular AGEs formation and accumulation in the body, and also by ingestion from food products. Exposure to AGEs on skeletal muscle cells leads to skeletal muscle dysfunctions including reductions of mass, contractile function, insulin sensitivity. These dysfunctions seem to be attributed to RAGE-induced inflammatory responses and deteriorations of cellular signaling transduction, including insulin/IGF-1 signaling. However, some therapeutic strategies, such as treatment with RAGE antagonists, AGEs inhibitors, phytochemicals can overcome the aggravating effects. Glycation research on skeletal muscle has not been sufficiently carried out, and further studies in the future, especially the elucidation of the effect of glycation stress on skeletal muscle and its underlying molecular mechanism, and the development of strategies on preventing the accumulation of AGEs in skeletal muscle, are desired.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Tatsuro Egawa[1*], Kohei Kido[2,3], Takumi Yokokawa[4], Mami Fujibayashi[5], Katsumasa Goto[6] and Tatsuya Hayashi[7]

1 Laboratory of Health and Exercise Sciences, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, Japan

2 Faculty of Sports and Health Science, Fukuoka University, Fukuoka, Japan

3 Institute for Physical Activity, Fukuoka University, Fukuoka, Japan

4 Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto, Japan

5 Faculty of Agriculture, Setsunan University, Osaka, Japan

6 Department of Physiology, Graduate School of Health Sciences, Toyohashi SOZO University, Aichi, Japan

7 Laboratory of Sports and Exercise Medicine, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, Japan

*Address all correspondence to: egawa.tatsuro.4u@kyoto-u.ac.jp

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