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Original article

Inhibition of advanced glycation endproduct formation in amino acids

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Abstract

The accumulation of advanced glycation endproducts (AGEs) in the body due to glycative stress is one of the factors that contribute to the progression of aging and age-related degeneration, such as reduced tissue elasticity, inflammation, and deteriorated physical function. To suppress glycation in the body, there are measures including suppressing postprandial hyperglycemia, preventing the formation of AGEs, and decomposing and excreting AGEs. In recent years, various plant materials have been recognized for their inhibitory effects on AGE formation, and are used in health foods, supplements, and skincare products that target glycation inhibition. Polyphenols and other plant materials have been identified as components that inhibit AGE formation. On the other hand, amino acids in food are important nutrients that also play a role in maintaining muscle and health by regulating protein and lipid metabolism. However, amino acids can quickly form AGEs through glycation, so when they coexist with proteins, they can act as a substitute and subsequently prevent the glycation of proteins. In this study, we used a protein-glucose glycation model with human serum albumin (HSA) and bovine collagen Type I (COL) to investigate the inhibitory effect of amino acids (23 types) on formation of the fluorescent AGEs (F-AGEs) and pentosidine. Inhibitory effects on F-AGE formation were observed for 17 amino acids in the HSA model and 20 amino acids in the COL model. Pentosidine formation was inhibited by 22 amino acids in both the HSA and COL model. The inhibitory rates of amino acids on both F-AGE and pentosidine formation were correlated between the HSA and COL models. No correlation was observed between the F-AGE and pentosidine formation inhibitory rate in the COL model. Based on these findings, it can be speculated that since amino acids have an inhibitory effect on AGE formation, their active intake may help prevent glycation-related aging.

***KEY WORDS*:** glycation reaction inhibition, amino acid, pentosidine, fluorescent AGEs

Introduction

The accumulation of advanced glycation endproducts (AGEs) in the body due to glycative stress is one of the factors that contribute to the progression of aging and chronic diseases, such as reduced tissue elasticity, induction of inflammation, and deteriorated physical function[1,2]. The suppression of glycative stress is called anti-glycation or glycation care. Glycation care can be done from the inside of the body by ingesting food materials or from the outside of the body using skin care products. To prevent glycation *in vivo*, there are measures such as suppressing postprandial hyperglycemia, inhibiting the formation of AGEs, and decomposing and excreting AGEs[3]. Aminoguanidine (AG) is known to have a glycation inhibitory effect[4,5]. However, the intake of AG has side effects, inducing liver dysfunction and vitamin B6 deficiency. For this reason, AG cannot be used in food or cosmetics. In recent years, AGE formation inhibitory effects have been recognized in various plant materials including tea[6], vegetables and herbs[7,8], and fruits[9], and so they are used as health foods, supplements, and skin care products focusing on glycation care. Components in these plant materials are identified as having an AGE formation inhibitory effect including polyphenols, *i.e.*, catechin, luteolin, and anthocyanin[10,11], and macrulin glycoside (3,4-dihydroxyphenyl-(2,4,6-trihydroxyphenyl)-ketone glycoside)[12]. In addition, whey from yogurt, a fermented food made from milk, has been reported to have an inhibitory effect on AGE formation[13]. The active ingredients in this work are presumed to be lactic acid or amino acids and peptides

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derived from milk proteins. Amino acids are important nutrients found in various foods; they help maintaining muscle and health functions by regulating the metabolism of protein and lipids, and are also involved in the taste of foods[14]. Amino acids are more reactive and quickly form AGEs through glycation than proteins. Therefore, when amino acids coexist with proteins, they may themselves be glycated, subsequently inhibiting the glycation of proteins. In addition, carnosine, a dipeptide composed of β-alanine and histidine, has been reported to have an inhibitory effect on AGE formation[15-17]. Amino acids are substances used by living organisms for life-sustaining activities and are highly safe substances. This study, aimed to verify the inhibitory effect of 23 types of amino acids on AGE formation. This effect was verified using a protein-glucose glycation model with human serum albumin (HSA) and type 1 collagen (COL).

Materials and Methods

1) Reagents

The amino acids used in the experiment were provided by Ajinomoto Co., Inc. (Kawasaki, Kanagawa, Japan). Reagents were purchased from the following manufacturers: Human serum albumin (HSA, lyophilized powder, ≥ 96%, agarose gel electrophoresis) was purchased from Sigma-Aldrich Japan (Tokyo, Japan). Collagen Type I (COL, derived from cowhide, pepsin-degraded) was purchased from Nippi (Tokyo). Aminoguanidine hydrochloride (AG) was purchased from Fujifilm Wako Pure Chemical Industries (Osaka, Japan). Other reagents were purchased as special grade or HPLC grade from Fujifilm Wako Pure Chemical Industries or Nacalai Tesque (Kyoto, Japan).

2) Sample

The following 23 types of amino acids were used as samples: Sodium aspartate hydrate (aspartic acid: Asp), glutamic acid (glutamic acid: Glu), lysine (lysine: Lys), arginine monohydrochloride (arginine: Arg), histidine hydrochloride (histidine: His), threonine (threonine: Thr), asparagine (asparagine: Asn), serine (serine: Ser), glutamine (glutamine: Gln), sodium tyrosine (tyrosine: Tyr), tryptophan (tryptophan: Trp), phenylalanine (phenylalanine: Phe), cysteine hydrochloride hydrate (cysteine: Cys), cystine (cystine: Cys-Cys), methionine (methionine: Met), glycine (glycine: Gly), isoleucine (isoleucine: Ile), leucine (Leu), valine (Val), proline (Pro), alanine (Ala), citrulline (Cit), and ornithine monohydrochloride (Orn). Amino acids were dissolved in water or ethanol solution, and then diluted to prepare sample solutions.

3) Protein-glucose glycation reaction model

To verify the inhibitory effect on glycation reaction, a protein-glucose glycation reaction model was used with reference to a previous report[18]. A 10 mmol/L amino acid solution was mixed with 0.1 mol/L phosphate buffer (pH 7.4) containing protein and glucose to prepare a reaction solution. The model protein and glucose concentrations were HSA 8 mg/mL, glucose 0.2 mol/L, and COL 1.2 mg/mL, and glucose 0.4 mol/L.

For the glycation reaction, a solution containing all of the phosphate buffer, protein solution, glucose solution, and sample solution (A), a solution containing purified water instead of the glucose solution in A (B), a solution containing sample dissolving solution instead of the sample solution in A (C), and a solution containing purified water instead of the glucose solution in C (D) were prepared and incubated at 60 °C. The incubation time was 40 hours for HSA and 10 days for COL.

4) Measurement of AGEs

F-AGEs were measured by centrifugal filtration of the glycation reaction solution after incubation using a 30K ultrafiltration membrane unit (Merck, Datmstadt, Germany) with reference to a previous report[18], and the protein fraction with a molecular weight of 30K or more was redissolved in 0.1 mol/L phosphate buffer (pH 7.4), and 200 µL was placed in a black microplate and measured by AGE-derived fluorescence (excitation wavelength 370 nm / fluorescence wavelength 440 nm). Pentosidine was measured by HPLC after mixing 50 µL of the glycation reaction solution with 6 N hydrochloric acid and hydrolyzing it at 105 °C for 18 hours, as previously reported[19].

5) Calculation of AGE formation inhibition rate

The AGE formation inhibition rate was calculated by the following formula for the inhibition rate of F-AGE and pentosidine formation (%), as previously reported[18]. AG was used as the positive control for the AGE formation inhibition.

$$\text{Inhibition rate (\%)} = \{1 - (A - B) / (C - D)\} \times 100$$

Statistical analysis

Measurements were expressed as mean ± standard deviation (SD) when measured three times, and as mean when measured twice. Correlation analysis was performed using Spearman's rank correlation coefficient. Results of statistical analysis were considered significant at a risk level of less than 5%.

Results

F-AGE formation inhibitory effect of amino acids

In the HSA-model, 17 of the 23 tested amino acids (concentration in reaction solution: 10 mmol/L) were found to have an F-AGE formation inhibitory effect (***Table 1***). The F-AGE formation inhibitory rate in the HSA-model was 2.0 ± 4.4% (Cit) at its lowest and 100.2 ± 0.4% (Cys-Cys) at its highest, a 50-fold difference. In the COL-model, 20 of the 23 tested amino acids were found to have an F-AGE formation inhibitory effect (***Table 1***). The F-AGE formation inhibitory rate in the COL-model was 5.1 ± 15.2% (Val) at

its lowest and 75.9 ± 2.2% (Cys-Cys) at its highest, a 15-fold difference.

A correlation was found between the F-AGE formation inhibitory rate of amino acids in the HSA-model and COL-model (p = 0.026, n = 16, ***Fig. 1***). The F-AGE formation inhibitory rate of 15 types of amino acids in the COL-model was higher than that in the HSA-model. No relationship was observed between the classification of amino acids (acidic, basic, neutral) and the F-AGE formation inhibitory effect (***Table 1***).

Pentosidine formation inhibitory effect of amino acids

The pentosidine synthesis inhibitory effect of 22 tested amino acids (concentration in reaction solution: 10 mmol/L) was observed in the HSA-model (***Table 2***). The pentosidine formation inhibitory rate in the HSA-model was 11.0% (Pro) at its lowest and 69.5% (His) at its highest, a 6-fold difference. In the COL-model, 22 out of 23 tested amino acids were observed to have a pentosidine formation inhibitory effect (***Table 2***). The pentosidine formation inhibitory rate in the COL-model was 2.7% (Pro) at its lowest and 101.6% (Cys-Cys) at its highest, a 38-fold difference. A correlation was observed between the pentosidine formation inhibitory rate of amino acids in the HSA-model and COL-model (p = 0.003, n = 21, ***Fig. 1***). The pentosidine formation inhibitory rate in the COL-model was higher than that in the HSA-model for 8 amino acids. No relationship was found between the classification of amino acids and their inhibitory effect on pentosidine formation (***Table 2***).

Table 1. Inhibition ratio (%) of fluorescent AGE formation by amino acids.

amino acid	classification	F-AGEs	
		HSA	COL
Asp	A	29.7 ± 3.7	48.6 ± 14.7
Glu	A	13.5 ± 6.5	42.4 ± 9.6
Lys	B	ND	ND
Arg	B	22.7 ± 7.0	21.7 ± 15.3
His	B	11.3 ± 1.8	ND
Thr	N	34.5 ± 4.2	30.0 ± 21.8
Asn	N	11.4 ± 2.2	24.3 ± 10.0
Ser	N	12.1 ± 3.7	34.5 ± 11.0
Gln	N	16.2 ± 3.3	28.1 ± 10.4
Tyr	N	ND	42.6 ± 13.2
Trp	N	41.0 ± 3.5	27.9 ± 5.3
Phe	N	ND	16.4 ± 15.4
Cys	N	77.1 ± 0.2	66.3 ± 7.1
Cys-Cys	N	100.2 ± 0.4	75.9 ± 2.2
Met	N	ND	7.9 ± 15.7
Gly	N	12.7 ± 2.8	36.2 ± 9.8
Ile	N	7.9 ± 4.5	8.2 ± 13.2
Leu	N	10.9 ± 7.3	32.3 ± 12.1
Val	N	4.7 ± 7.6	5.1 ± 15.2
Pro	N	ND	5.3 ± 7.7
Ala	N	16.4 ± 3.7	47.2 ± 8.8
Cit	N	2.0 ± 4.4	28.1 ± 8.6
Orn	N	6.4 ± 2.0	ND

Data; mean ± standard deviation (n = 3), A; acidic, B; basic, N; neutral, ND, not effective; HSA, human serum albumin-glucose glycation model; COL, collagen-glucose glycation model; AGE, advanced glycation endproduct; F-AGEs, fluorescent AGEs.

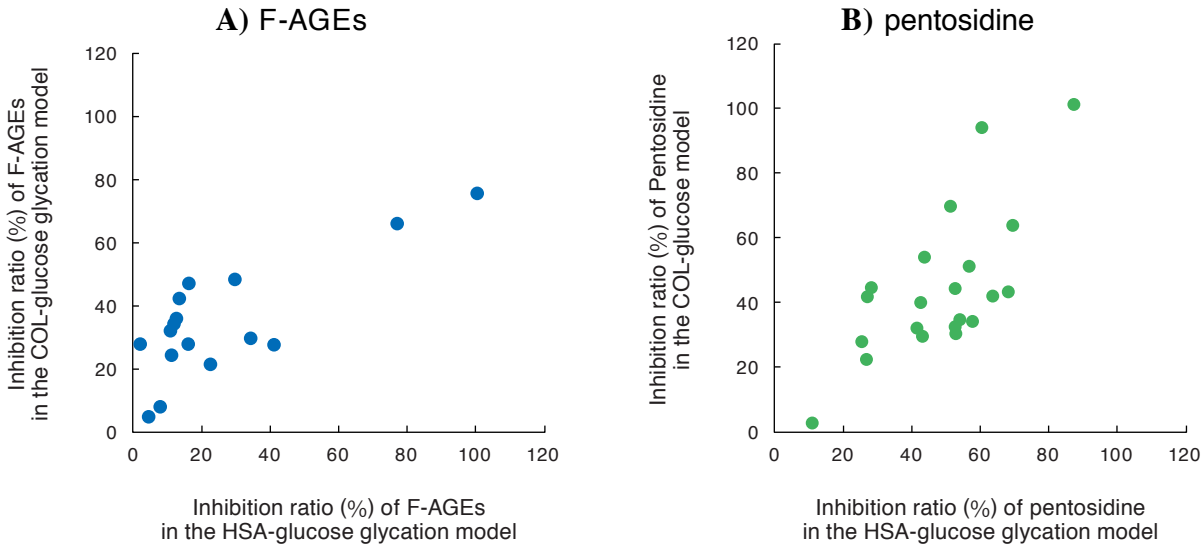

Fig. 1. **Correlation between two protein glycation models in the AGE inhibition rate by amino acids.**

A: F-AGEs (n = 16), **B**: pentosidine (n = 21), Samples with ND results were excluded from the plot. ND, not effective; COL; collagen-glucose glycation model; AGE, advanced glycation endproduct; F-AGEs, fluorescent AGEs.

Table 2. Inhibition ratio (%) of pentosidine formation by amino acids.

amino acid	classification	Pentsidine	
		HSA	COL
Asp	A	52.7	44.4
Glu	A	52.7	32.5
Lys	B	27.2	41.8
Arg	B	28.3	44.6
His	B	69.5	64.0
Thr	N	56.7	51.2
Asn	N	63.6	42.1
Ser	N	57.8	34.1
Gln	N	43.1	29.5
Tyr	N	16.6	ND
Trp	N	ND	73.1
Phe	N	43.7	54.1
Cys	N	60.5	94.4
Cys-Cys	N	87.2	101.6
Met	N	42.5	39.9
Gly	N	68.1	43.5
Ile	N	25.4	27.9
Leu	N	41.4	32.1
Val	N	26.8	22.4
Pro	N	11.0	2.7
Ala	N	53.9	34.7
Cit	N	52.9	30.6
Orn	N	51.3	69.9

Data: mean (n = 2), A; acidic, B; basic, N; neutral, ND; not effective, HSA; human serum albumin-glucose glycation model, COL; collagen-glucose glycation model.

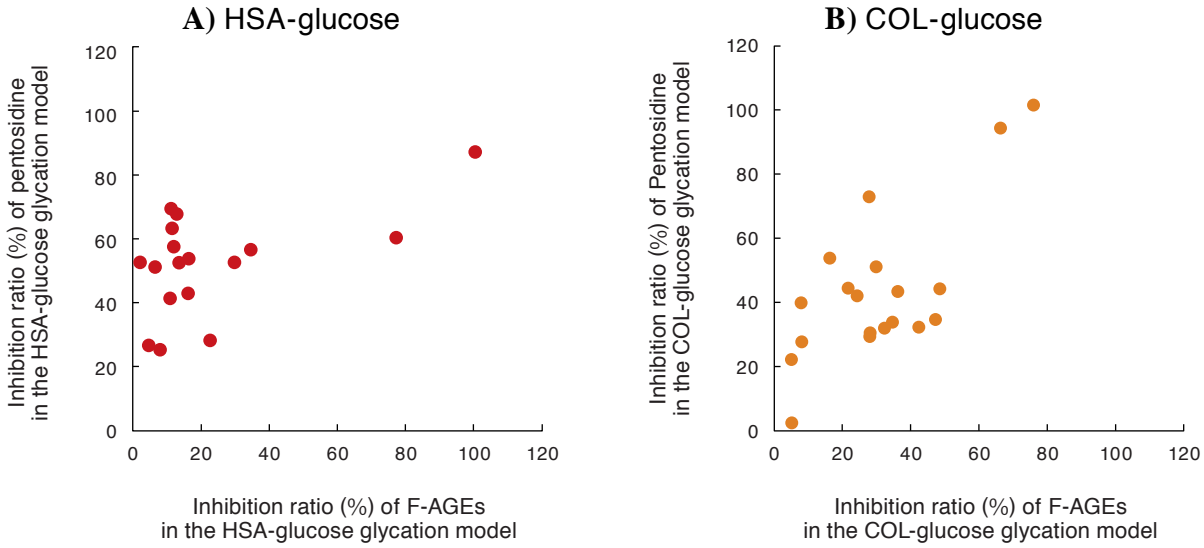

Fig. 2. **Correlation between F-AGE and pentosidine inhibition rates by amino acids in each glycation protein model.**

A: HSA-glucose glycation model (n = 17), **B**: COL-glucose glycation model (n = 19), Samples with ND results were excluded from the plot. ND, not effective; HSA, human serum albumin-glucose glycation model; COL; collagen-glucose glycation model; AGE, advanced glycation endproduct; F-AGEs, fluorescent AGEs.

Discussion

Amino acids inhibit AGE formation

Amino acids themselves react with glucose and are glycated. Therefore, the reaction solution of the protein-glucose glycation reaction model contains not only the model protein but also AGEs derived from the amino acids added as samples. In the evaluation system used in this experiment, the reaction solution after incubation was ultrafiltered to remove low molecular weight substances of 30 kDa or less, and the inhibitory effect of the sample amino acids on the AGE formation in the model protein was evaluated. The concentration of amino acids added to the reaction system was 10 mmol/L, 1/40 of the glucose concentration (0.4 mol/L), on reducing the reactivity of the model protein and glucose was slight. In verifying the inhibitory effect of amino acids on AGE formation using the protein-glucose glycation model, the inhibitory effect of the F-AGE and pentosidine was observed. The inhibitory effect on AGE formation has been observed in extracts of vegetables [7] fruits [9], various flavonoids [11], ferulic acid [20], and iridoid [21] contained in these extracts. However, the mechanism by which these substances inhibit AGE formation is unclear. On the other hand, aminoguanidine inhibits AGE formation by binding to the carbonyl group of α-diketones such as 3-deoxyglucosone (3DG), glyoxal (GO), and methylglyoxal (MGO), which are intermediates in the glycation reaction [4]. Arginine is presumed to have a similar effect to AG [22]. It has been reported that carnosine (β-alanyl-histidine), homocarnosine (γ-aminobutyryl-histidine), anserine, Ala, His, and glutathione inhibit the AGE formation by inhibiting the early stage of glycation [15-17].

In the protein-glucose glycation model, the carbonyl group of glucose reacts with the amino group of the protein to form a Schiff base, and the imine double bond is transferred to produce Amadori compounds, which then lead to AGE formation through glycation intermediate formation, *i.e.*, 3DG, GO, MGO, glyceraldehyde, and glutaraldehyde [1]. In this experiment, F-AGEs and pentosidine were measured as AGEs. The measured F-AGEs are the total amount of AGEs that have fluorescence (excitation wavelength 370 nm, fluorescence wavelength 440 nm), and include crossline [23], pyrropyridine [24,25], vesperlisine [26,27], and argpyrimidine [28]. These AGEs are generated from different glycation pathways [29]. The AGE formation inhibitory effect verified in this study varied depending on the type of amino acid, with a 50-fold difference in F-AGEs and a 38-fold difference in pentosidine. The mechanism by which amino acids inhibit AGE formation is not only through the inhibition of the formation of Amadori compounds and glycation intermediates that are produced in the early stages of glycation reactions [17], but also through the possibility of inhibiting different AGE formation pathways depending on the type of amino acid.

Differences in the AGE formation inhibitory effects of amino acids on HSA and COL

The inhibitory rates of F-AGE and pentosidine formation by amino acids were correlated in both the HSA-model and the COL-model. The F-AGE formation inhibitory effect of spice extracts has already been verified using the HSA-model and COL-model [30]. No correlation was observed between the F-AGE formation inhibitory effect of spice extracts in the HSA-model and the COL-model. It is assumed that polyphenols are involved in the F-AGE formation inhibitory effects of spices. Yogurt whey was found to have inhibitory effects on the formation of F-AGEs, pentosidine, CML, GO, and MGO

in the HSA-model[13]. Correlations were observed between inhibitory rates of F-AGEs and pentosidine, F-AGEs and CML, and GO and MGO formation in yogurt whey. It is assumed that the AGE formation inhibitory effect of yogurt whey is due to amino acids and peptides derived from milk proteins. The correlation between the F-AGE formation inhibition rate and the pentosidine formation inhibition rate by amino acids may be less affected by differences in protein types compared the effect of polyphenols.

The usefulness of amino acids in inhibiting the AGE formation

Amino acids are important nutrients found in a variety of foods and are also components with health functions such as regulating protein and lipid metabolism and maintaining muscle mass. Amino acids also affect the taste of food, and extracts from vegetables, seafood, or meat are widely used in dishes worldwide as soups and stocks ("dashi": broth)[31, 32]. For this reason, the AGE formation inhibitory effect of amino acids can be easy to incorporate into daily diets. The accumulation of AGEs due to glycation promotes polymerization through cross-linking of proteins, reducing the elasticity of protein tissue[33]. Yogurt whey, which contains amino acids and peptides derived from milk, inhibits AGE formation, prevents protein polymerization, and reduces protein browning[13]. The onset and progression of Alzheimer's disease and Parkinson's disease are related to the aggregation of amyloid β and the fibrillation of α-synuclein[34, 35], and the accumulation of AGEs due to protein glycation, possibly accompanied by cross-linking and polymerization, is involved in the promotion of fibrosis[36]. Amino acids pass through the blood-brain barrier (BBB)[37] and may contribute to the inhibition of glycation in brain tissue. In the future, the challenge will be to understand the tissue migration and distribution of water-soluble and lipid-soluble amino acids, leveraging their unique characteristics, and to explore the optimal amino acid composition as a preventive measure against diseases involving glycation.

Research limitation

Amino acids are found in all foods and are essential for life, so they are considered highly safe substances. Consequently, the AGE formation inhibitory effect of amino acids in this study was verified in *in vitro* testing. However, the effectiveness of amino acids in inhibiting AGE formation in the body needs to be verified in human clinical trials.

Conclusion

As a result of verifying the inhibition of AGE formation by 23 types of amino acids, F-AGE formation inhibitory effect was observed in 17 types in the HSA-model and 20 types in the COL-model. Additionally, a pentosidine inhibitory effect was observed in 22 types each in both the HSA and COL models. Active intake of amino acids may help prevent of age-related degeneration of the body due to glycation.

Conflict of interest declaration

Ajinomoto Co., Inc. provided amino acid samples and provided research funding for this study.

Acquisition of competitive funds

None in particular

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