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# Maltitol endows foods with lower 3-deoxyglucosone content and less RAGE agonism as a sweetener against sucrose

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## Abstract

***Objective*:** Sweeteners have the potential to promote the production of advanced glycation endproducts (AGE), which influence human health and aging and have been implicated in diseases such as diabetic vascular complications, Alzheimer's disease, and cancer. Maltitol is a polyol used as a sweetener in the food industry. In this study, we evaluated the effects of maltitol on the formation of a potent glycation intermediate, 3-deoxyglucosone (3-DG), and AGE and on receptor for AGE (RAGE) signaling in various food models.

***Methods*:** Biscuit, muffin, pudding, bean compote, doughnut, chicken dumpling, bread, and broiled sauce were used as model foods prepared with or without sucrose/MS-17 (a mixture of sucrose and maltitol)/maltitol. The resultant materials were assayed for 3-DG, AGE fluorescence, $N^{\varepsilon}$-(carboxymethyl) lysine (CML), pentosidine, and RAGE agonism/antagonism.

***Results*:** Biscuit, muffin, doughnut, and bread samples treated with maltitol contained significantly less 3-DG than samples treated with sucrose. Although the levels of AGE fluorescence, CML, and pentosidine did not differ significantly between sucrose and maltitol treatments in the model foods, maltitol endowed significantly less agonistic effects on RAGE signaling in the 4 model foods with lower 3-DG content.

***Conclusion*:** Compared with sucrose, maltitol is a functional sweetener that may exhibit more beneficial effects on human health.

***KEY WORDS*:** Maltitol, Advanced glycation endproducts, RAGE, 3-Deoxyglucosone, Sweetener

## Introduction

Protein glycation via the Maillard reaction involves multi-step, spontaneous reactions initiated by the non-enzymatic reaction between carbonyl groups of sugars and free amino groups of proteins. This is followed by the formation of Schiff bases and then by Amadori rearrangement to generate reactive intermediates, which undergo irreversible reactions, eventually yielding structurally divergent products known collectively as advanced glycation endproducts (AGE) [1), 2)]. A variety of intermediates and AGE have been identified, including 3-deoxyglucosone (3-DG) [3)], pentosidine, and $N^{\varepsilon}$-(carboxymethyl) lysine (CML). Glycation alters the structure of proteins, leading to their dysfunction. AGE accumulation in the body has been linked to several age-related diseases. Glycated proteins induce cytotoxicity by binding to the receptor for AGE (RAGE), and AGE-RAGE interactions have been implicated in various pathologic conditions such as diabetes, arteriosclerosis, osteoporosis, and Alzheimer's disease [4)]. Thus, numerous researches have been directed to controlling AGE formation and action for health promotion, anti-aging, and overcoming lifestyle-related disease. AGE and their intermediates are also formed in foods during heating and are then absorbed from the intestine [5-8)].

Maltitol is a hydrogenated carbohydrate used in the production of sugar-free or sugarless confectionery, chewing gum, and chocolate. It is considered by manufacturers of foods to be an interesting ingredient that does not induce high postprandial increases in blood glucose. Accordingly, maltitol can be used as an alternative to sucrose in sugar-free or sugarless foodstuffs. It has low-energy [9)], low-glycemic [10)], low-insulinemic [11)], and non-cariogenic [12)] properties and can be produced from maltose via catalytic hydrogenation [13-16)]. Maltitol is only partially hydrolyzed by intestinal brush-border disaccharidase and thus is poorly absorbed through the intestinal mucosa [17-21)]; the products of its partial hydrolysis in the intestine are glucose and sorbitol [13)]. In addition, maltitol may have inhibitory effects on glycation [22)] and tumorigenesis [23)]

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and a beneficial effect on cognitive function [24]. The maximum no-effect level (NOEL) is reported to be 0.3 g/kg body weight for both males and females, and the excessive consumption of maltitol may produce laxative effects [25].

This study evaluated the effects of maltitol on the formation of 3-DG and AGE in various model foods through comparison with the effects of sucrose. The effect of maltitol on RAGE signaling was also compared in with the sucrose-treated model foods.

## Materials and Methods

### Chemicals

Sucrose (granulated sugar) was purchased from Mitsui Sugar Co., Ltd. (Tokyo, Japan), and maltitol ("MALTITOL POWDER WHOLE CRYSTALLINE MALTITOL - UENO 60M") and MS-17 ("MALTITOL - BASED SUGAR PREPARATION: MS-17": sugar: maltitol = 83%:17%) were obtained from Ueno Fine Chemicals Industry, Ltd. (Osaka, Japan).

### Food models and treatment with sucrose, maltitol, or MS-17

Eight food models were prepared with the following commonly used cooking methods: biscuit (180°C, 15 min), muffin (170°C, 20 min), pudding (85°C, 20 min), bean compote (85°C, 15 min), doughnut (180°C, 30 sec), chicken dumpling (100°C, 20 min), bread (150°C, 35 min), and broiled sauce (63°C, 20 min). The ingredients in these model foods are shown in ***Table 1***. In place of sugars, sucrose, maltitol, or MS-17 was added at the given percentage; sugar was omitted in the control without sweetener. Two grams of each food model was homogenized in 20 mL of 0.5 M phosphate buffer (pH 7.4), passed through a VIVA SPIN 20 (Sartorius Stedim Biotech S.A., Göttingen, Germany), and divided into a higher molecular weight (MW) fraction (≥10,000) and a lower MW fraction (<10,000). The higher MW fraction underwent hydrolysis in 2 mL of 6 M HCl for 16 hours at 110°C under nitrogen gas and was neutralized with 5 M NaOH. The neutralized solutions were filtered through a Minisart (Sartorius) and used for AGE determination and RAGE signaling assay. The lower MW fraction was used for 3-DG determination.

### 3-DG measurement

3-DG concentration was determined as described elsewhere [26]. 2,3-Pentanedione was added as an internal standard. TSK-gel ODS-80Ts (46 × 150 mm, Tosoh Corporation, Tokyo, Japan) was used in high-performance liquid chromatography.

### Measurement of AGE fluorescence

Aliquots of the neutralized higher MW model food fractions were placed in the wells of a 96-well black microplate and excited at 380 nm. Emission was scanned at 400-600 nm in a Varioskan Flash microplate reader (Thermo Fisher Scientific Inc., MA, USA). Perylene was used as the standard, in which emission from 410 to 600 nm was recorded upon excitation at 386 nm. Relative fluorescence was calculated according to the following formula:

Sum of sample fluorescence at 400-600 nm / sum of perylene fluorescence at 410-600 nm.

***Table 1. Ingredients in the model foods used in this study***

| Model food | Ingredients (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Egg | Milk | Flour | Bean | Soy sauce | Chicken | Corn starch | Sugar | Other |
| Biscuit | — | 7.0 | 27.0 | — | — | — | 27.0 | 15.0 | 24.0 |
| Muffin | 25.0 | — | 25.0 | — | — | — | — | 25.0 | 25.0 |
| Pudding | 36.0 | 50.0 | — | — | — | — | — | 13.0 | 1.0 |
| Bean compote | — | — | — | 62.9 | 0.4 | — | — | 36.7 | 0.0 |
| Doughnut | 14.0 | 15.0 | 46.0 | — | — | — | — | 15.0 | 10.0 |
| Chicken dumpling | — | — | — | — | — | 83.0 | — | 8.0 | 9.0 |
| Bread | — | 1.8 | 49.0 | — | — | — | — | 10.0 | 39.2 |
| Broiled sauce | — | — | — | — | — | — | — | 25.0 | 75.0 |

### *CML measurement*

CML was measured with a CML enzyme-linked immunosorbent assay kit (CycLex Co., Ltd., Nagano, Japan) according to the manufacturer's instructions.

### *Pentosidine measurement*

Pentosidine was measured with an FSK pentosidine enzyme-linked immunosorbent assay kit (Fushimi Pharmaceutical Co., Ltd., Kagawa, Japan) according to the manufacturer's instructions.

### *Luciferase reporter assay*

Rat C6 glioma cells that had been stably transformed with an expression plasmid containing full-length human RAGE complementary DNA and a firefly luciferase reporter gene under the control of the nuclear factor κB (NFκB) promoter [27] were used. After a 24-hour preincubation in Dulbecco's modified Eagle's medium supplemented with 0.1% fetal bovine serum, the cells were stimulated with the aliquots of the higher MW model food fractions in the presence or absence of glyceraldehyde-derived AGE-bovine serum albumin (BSA) (glycer-AGEs) for 4 hours. Luciferase activity was determined with a Luciferase Assay System (Promega Co., WI, USA) and measured in a luminometer (Fluoroskan Ascent FL; Labotal Scientific Equipment Ltd., Abu Gosh, Israel).

### *Statistical analysis*

Statistical analysis was performed using the Student's *t* test. A p value smaller than 0.05 was considered significant.

## *Results*

### *Maltitol lowers 3-DG contents in biscuit, muffin, doughnut, and bread.*

Eight model foods were prepared with sucrose or maltitol and assayed for 3-DG. As shown in ***Fig. 1***, biscuit, muffin, doughnut, and bread prepared with maltitol had 3-DG contents significantly lower than that of their counterparts prepared with sucrose. In bread, the 3-DG lowering effect of MS-17, a mixture of sucrose and maltitol, was between that of sucrose and maltitol. No significant difference was found between sucrose and maltitol in pudding, bean compote, or broiled sauce. 3-DG was not detected in chicken dumpling.

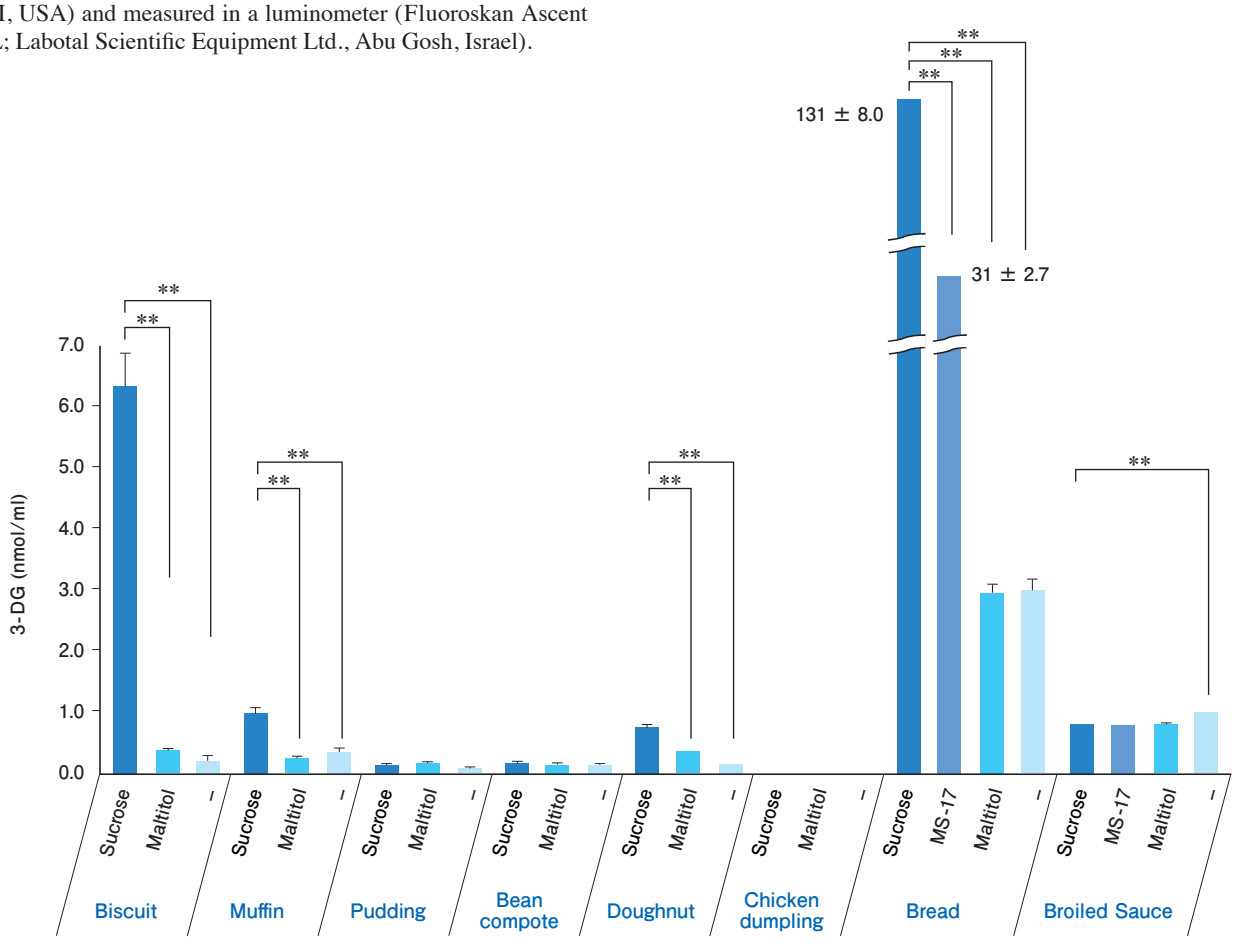


***Fig.1.***

3-Deoxyglucosone (3-DG) levels in model foods treated with or without (-) sucrose/maltitol. The conditions of the treatments are described in the Materials and Methods. Values are expressed as means ± standard error. The values of broiled sauce treated with sucrose, MS-17, and maltitol are related to the value without sweetener, which is equivalent to 281 (nmol/g). -, treated without sweetener. $^{**}p < 0.01$ (vs. the sucrose-treated food) (n = 3-9).

### *Evaluation of AGE formation in model foods*

To know whether maltitol affected AGE formation during food preparation, we examined the levels of AGE fluorescence, CML, and pentosidine in the model foods. As shown in ***Table 2***, these values were essentially invariant between sucrose- and maltitol-treated biscuit, muffin, pudding, bean compote, doughnut, and chicken dumpling, and among sucrose-, maltitol- and MS-17-treated bread and broiled sauce.

### *Maltitol had a less agonistic effect on RAGE signaling compared with that of sucrose.*

We next examined whether sucrose and maltitol treatments of model foods affected RAGE signaling using a reporter system in which the firefly luciferase gene was placed under the control of a NF $\kappa$B promoter in C6 glioma cells. Reporter activation in this system is dependent on ligand-RAGE interaction, as evidenced by (1) induction by AGE, (2) inhibition by small interfering RNA against RAGE messenger RNA, (3) inhibition by transfection of dominant-negative RAGE, and (4) neutralization by soluble RAGE[27].

As shown in ***Fig. 2*** A-H, glycer-AGEs induced luciferase activity that was approximately 3-fold that of control BSA. Samples with higher luciferase activity than that of the BSA control were considered agonistic, whereas in the coexistence of glycer-AGEs, those that showed lower luciferase activity compared with that of glycer-AGEs alone were considered antagonistic. Biscuit (see *Fig. 2A*), muffin (see *Fig. 2B*), pudding (see *Fig. 2C*), bean compote (see *Fig. 2D*), doughnut (see *Fig. 2E*), and bread (see *Fig. 2G*) showed statistically significant increases in luciferase activity compared with that in the BSA control. Statistically significant increases were also found in the coexistence of glycer-AGEs in these foods compared with the value with glycer-AGEs alone, indicating that they had agonistic effects on RAGE signaling. Broiled sauce (see *Fig. 2H*) had an agonistic effect when added alone but not when coexisting with AGE. Sucrose- and maltitol-treated chicken dumpling (see *Fig. 2F*) caused no significant changes in the presence or the absence of AGE.

Maltitol had less agonistic effects than those of sucrose in biscuit, muffin, and doughnut in the presence of AGE (see *Fig. 2A, B, and E*) and in bread with or without AGE (see *Fig. 2G*). These 4 model foods were those that had lower 3-DG content when prepared with maltitol. None of the 8 food models exhibited cell toxicity at the doses tested (data not shown).

***Table 2. Levels of advanced glycation endproducts (AGE) fluorescence, $N^{\varepsilon}$-(carboxymethyl lysine (CML), and pentosidine***

| Model food | | AGE fluorescence (nmol/g) | CML (nmol/g) | Pentosidine (nmol/g) |
|---|---|---|---|---|
| Food | Sweetener | | | |
| Biscuit | Sucrose | 39 ± 8.2 | 823 ± 28 | 6.2 ± 1.9 |
| | Maltitol | 32 ± 4.3 | 861 ± 9 | 8.5 ± 81.2 |
| | – | 33 ± 1.8 | 789 ± 29 | 5.0 ± 0.8 |
| Muffin | Sucrose | 37 ± 0.8 | 540 ± 22 | 1.1 ± 0.2 |
| | Maltitol | 36 ± 2.0 | 532 ± 12 | 1.2 ± 0.2 |
| | – | 30 ± 2.8 | 466 ± 44 | 1.0 ± 0.2 |
| Pudding | Sucrose | 70 ± 3.5 | 791 ± 26 | 1.4 ± 0.4 |
| | Maltitol | 81 ± 8.1 | 764 ± 24 | 2.0 ± 0.5 |
| | – | 104* ± 8.6 | 892 ± 32 | 1.9 ± 0.5 |
| Bean compote | Sucrose | 45 ± 2.7 | 777 ± 27 | 4.7 ± 1.3 |
| | Maltitol | 65 ± 7.6 | 784 ± 17 | 2.8 ± 0.5 |
| | – | 52 ± 8.9 | 821 ± 26 | 5.0 ± 0.4 |
| Doughnut | Sucrose | 23 ± 1.5 | 680 ± 16 | 1.8 ± 0.3 |
| | Maltitol | 23 ± 1.9 | 741 ± 23 | 1.3 ± 0.1 |
| | – | 30* ± 1.1 | 813* ± 34 | 2.2 ± 0.7 |
| Chicken dumpling | Sucrose | 27 ± 0.7 | 977 ± 77 | 1.4 ± 0.1 |
| | Maltitol | 26 ± 1.9 | 950 ± 72 | 1.4 ± 0.3 |
| | – | 27 ± 2.1 | 941 ± 57 | 1.23 ± 0.3 |
| Bread | Sucrose | 32 ± 1.6 | 553 ± 4 | 0.61 ± 0.11 |
| | MS-17 | 30 ± 4.3 | 527 ± 20 | 1.85 ± 0.91 |
| | Maltitol | 35 ± 1.5 | 576 ± 30 | 0.38 ± 0.09 |
| | – | 27 ± 2.5 | 489* ± 19 | 0.79 ± 0.12 |
| Broiled sauce | Sucrose | 0.034 ± 0.004 | 1.2 ± 0.05 | 0.0004 ± 0.00001 |
| | MS-17 | 0.030 ± 0.004 | 1.1 ± 0.04 | 0.0004 ± 0.00004 |
| | Maltitol | 0.030 ± 0.003 | 1.2 ± 0.02 | 0.0002* ± 0.000003 |
| | – | 0.036 ± 0.003 | 1.2 ± 0.02 | 0.0003**± 0.00004 |

Model foods were treated as described in Materials and Methods. AGE fluorescence was recorded at 400-600 nm upon excitation at 380 nm, related to the value with 10 μM perylene, and expressed in nanomoles per milliliter. CML and pentosidine levels were determined with enzyme-linked immunosorbent assay. Values are expressed as means ± standard error. -, treated without sucrose/maltitol. $^{**}p < 0.01$ (vs. the sucrose-treated food), $^{*}p < 0.05$ (vs. the sucrose-treated food) (n = 3-9).

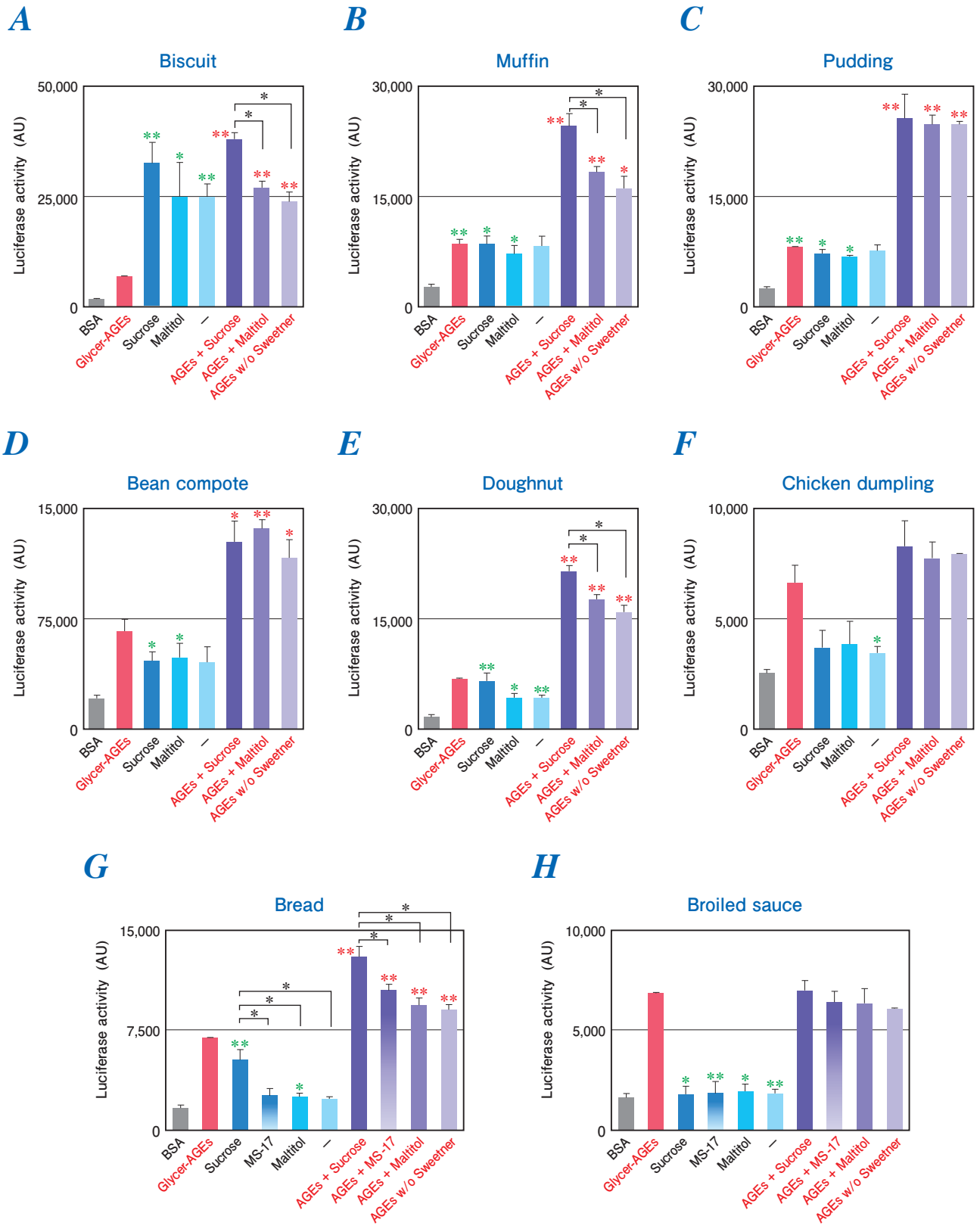


*Fig.2.*

Luciferase activity of the C6 glioma cells exposed to model foods prepared with or without (-) sweetener. The model foods tested were biscuit (*A*), muffin (*B*), pudding (*C*), bean compote (*D*), doughnut (*E*), chicken dumpling (*F*), bread (*G*), and broiled sauce (*H*). BSA, bovine serum albumin (50 μg/mL) used as a negative control; glycer-AGEs, glyceraldehyde-derived AGE-BSA (50 μg/ml) used as a positive control; AGE + sucrose, cells incubated with glycer-AGEs and food prepared with sucrose; AGE + MS-17, cells incubated with glycer-AGEs and food prepared with MS-17; AGE + Maltitol, cells incubated with glycer-AGEs and food prepared with maltitol; AGE w/o Sweetener, cells incubated with glycer-AGEs and food prepared without sweetener. Values are expressed as means ± standard error. $^{**}p < 0.01$ (*vs*. food prepared with sucrose); $^{*}p < 0.05$ (*vs*. food prepared with sucrose); $^{**}p < 0.01$ (*vs*. BSA); $^{*}p < 0.05$ (*vs*. BSA); $^{**}p < 0.01$ (*vs*. glycer-AGEs); $^{*}p < 0.05$ (*vs*. glycer-AGEs) (n = 3-6).

## Discussion

This study was conducted to determine the effects of maltitol, a polyol sweetener, on 3-DG and AGE formation and RAGE signaling in 8 food models. The results indicate that maltitol endowed 4 of the 8 foods with lower 3-DG content and less agonistic RAGE activity. The food models that consistently displayed lower 3-DG levels and less RAGE agonism were biscuit, muffin, doughnut, and bread. Their common features were (1) inclusion of flour as the major ingredient (see *Table 1*), and (2) cooking temperature above 150°C. The food models that lacked 3-DG-lowering and RAGE signal-lowering effects contained no flour and were cooked at temperatures below 100°C. It is, therefore, reasonable to posit that the higher the 3-DG content of a food the greater the number of products causing RAGE activation. When gliadin, a main component of flour, underwent similar analysis, 3-DG content in maltitol-treated gliadin was lower than that in sucrose-treated gliadin, whereas RAGE-dependent reporter activity was not different between the two (data not shown). This result suggests that the 3-DG-lowering and RAGE signal-lowering effects of maltitol might be independent phenomena or that components of flour other than gliadin might account for the maltitol effects in the model foods. Nevertheless, maltitol can be regarded as a sweetener that yields less noxious food products than those produced by sucrose (see *Fig. 2*).

Koschinsky *et al.*[28] have estimated that the total amount of orally absorbed AGE found in blood is equal to approximately 10% of that estimated to be present in an ingested meal, and that only 30% of circulating AGE is excreted in the urine over the subsequent 48 hours. Recently, Munesue *et al.*[29] have demonstrated that certain food-derived AGE exhibit agonistic/antagonistic effects on RAGE signaling. Accordingly, levels of AGE fluorescence, CML, and pentosidine in the food models were determined in the present study. However, no significant differences were revealed by these assays among sucrose-, maltitol- or MS-17-treated foods. The RAGE signal-lowering effect of maltitol may be ascribed to currently unassayable or hitherto unidentified AGE structures or non-AGE ligands of RAGE.

Bread seems to exemplify the effects of maltitol. The 3-DG content of maltitol-treated bread was approximately 10-fold and 43-fold lower than that in MS-17- and sucrose-treated breads, respectively (see *Fig. 1*). The capability of maltitol to induce RAGE signaling was potent in the following order: bread prepared with sucrose > MS-17 > maltitol (see *Fig. 2*). Serum 3-DG levels are reportedly 0.20 ± 0.05 nmol/mL in normal humans and 0.35 ± 0.11 nmol/mL in diabetic patients[26]. Assuming that the blood volume of the average adult is 4,500 mL and that a sliced of bread weighs 60 g, serum 3-DG level should reach the level of a diabetic patient when 1 slice of bread prepared with sucrose, 5 slices of breads prepared with MS-17, or 54 slices of breads prepared with maltitol are consumed.

## Conclusion

In this study, we have shown that maltitol yields lower 3-DG content and has a less agonistic effect on RAGE signaling, especially in flour-rich foods. We thus conclude that compared with sucrose, maltitol is a sweetener that provides superior health benefits.

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