RESEARCH ARTICLE

The regulation of jejunal induction of the maltase–glucoamylase gene by a high-starch/low-fat diet in mice

Kazuki Mochizuki, Kazue Honma, Masaya Shimada and Toshinao Goda

Laboratory of Nutritional Physiology, The University of Shizuoka, Graduate School of Nutritional and Environmental Sciences and Global COE, Shizuoka, Japan

Received: September 24, 2009
Revised: December 2, 2009
Accepted: December 6, 2009

Maltase and glucoamylase are derived from the same mRNA and are responsible for digestion of starch in the small intestine. Their jejunal activities in rodents are induced by a high-starch/low-fat (HS)-diet. However, it is unknown whether jejunal expression of the maltase–glucoamylase (*Mgam*) gene is enhanced by the HS-diet. In this study, we found that jejunal *Mgam* mRNA was increased by a HS-diet in mice. We showed that the HS-diet increased acetylation of histones, bindings of a coactivator, Creb binding protein (CREBBP), and the transcriptional factors caudal type homeobox 2 (CDX2) and HNF1 homeobox (HNF1) in the promoter/enhancer and transcriptional regions of *Mgam* gene. This suggests that the increase in the jejunal activity of maltase and glucoamylase caused by a HS-diet in mice is regulated at the mRNA level through histone acetylation and binding of CREBBP, CDX2 and HNF1 in the promoter/enhancer and transcriptional regions of *Mgam* gene.

Keywords:
Chromatin / High-starch/low-fat diet / Histone acetylation / Maltase–glucoamylase / Small intestine

1 Introduction

After oral intake of carbohydrates, starch is digested to α-limit dextrin, maltotriose and maltose by α-amylase in saliva and pancreatic fluid. α-Limit dextrin and maltotriose are subsequently digested to glucose from the non-reducing end of the substrates by disaccharidases such as maltase–glucoamylase complex and sucrase–isomaltase complex, which are expressed in the brush border membrane of the small intestine. Particularly, glucoamylase and maltase greatly contribute to maltooligosaccharide digestion and it is known that glucoamylase prefers longer maltooligosaccharide substrates and maltase prefers shorter substrates. Sucrose is digested to glucose and fructose by sucrase [1–4]. These monosaccharides are then absorbed by the enterocytes through hexose transporters and transported to the portal vein [5].

It is known that rapid digestion of carbohydrates in the gastrointestinal tract results in high postprandial glucose and insulin levels in blood. Several studies have shown that inhibiting disaccharidases with inhibitors such as acarbose, miglitol and voglibose reduces postprandial hyperglycemia and ameliorates diabetes [6, 7]. Thus, it is important to regulate the activities and gene expression of disaccharidases in the small intestine to inhibit postprandial hyperglycemia/hyperinsulinemia.

Several studies have shown that the jejunal activities of maltase, glucoamylase, sucrase and isomaltase were higher in rats fed a high-starch/low-fat (HS) diet than in those fed a low-starch/high-fat (LS) diet [8, 9]. This suggests that disaccharidase activity in rats is increased by a diet containing a high-energy percentage derived from starch. We have previously demonstrated that feeding rodents a HS-diet increased the jejunal expression of the sucrase-isomaltase (*Si*)

Correspondence: Dr. Toshinao Goda, Laboratory of Nutritional Physiology, School of Food and Nutritional Sciences, The University of Shizuoka, 52-1 Yada, Shizuoka-shi, Shizuoka 422-8526, Japan
E-mail: gouda@u-shizuoka-ken.ac.jp
Fax: 81-54-264-5565

Abbreviations: ChIP, chromatin immunoprecipitation; **CT,** cycle threshold; **HS,** high starch/low fat; **LS,** low starch/high fat

gene, which is a single gene that expresses both the sucrase and the isomaltase protein [10–12]. It has also been shown that expression of the *Si* gene is regulated by nuclear transcriptional factors such as caudal type homeobox 2 (CDX2) and HNF1 homeobox (HNF1) in Caco-2 cells, an intestinal cell line [13]. In addition, we have demonstrated that CDX2 and HNF1 are not only strongly bound to the promoter region of the *Si* gene in mice, but also that binding is increased by a HS-diet [11]. Furthermore, we revealed that histone acetylation on the *Si* gene, which is one of the histone modifications that have a central role in the regulation of transcription, was increased by a HS-diet in mice [11]. Hyperacetylation of histones H3 and H4 is associated with the euchromatin region on the genome [14, 15] and histone acetylation promotes transcription through recruiting the transcriptional complex on the target genes [16]. Therefore, the increase in *Si* gene expression caused by a HS-diet in mice is regulated not only by binding of transcriptional factors such as CDX2 and HNF1, but also by recruiting the mRNA transcriptional complex on acetylated histones of the *Si* gene.

Little is known about the transcriptional regulation of the maltase–glucoamylase (*Mgam*) gene, the gene that expresses both the maltase and the glucoamylase protein, because the gene has only recently been cloned [2–4]. As maltase and glucoamylase have a greater contribution to intestinal starch digestion than sucrase and isomaltase it is necessary to determine whether a HS-diet increases jejunal expression of the *Mgam* gene in rodents, and to investigate its underlying mechanism. This may give us better understanding of the induction of postprandial hyperglycemia/hyperinsulinemia after intake of starch [5, 17].

In this study, we examined whether the induction of maltase and glucoamylase activities by feeding mice a HS diet is regulated at the mRNA level through increased histone acetylation, binding of the coactivator CREBBP, which is known to bind to the acetylated histones and nuclear transcriptional factors to mediate the recruitment of the transcriptional complex [18], and binding of nuclear transcriptional factors (CDX2 and HNF1).

2 Materials and methods

2.1 Animals

Seven week old male mice of the C57BL/6J strain (Japan SLC, Hamamatsu, Japan) were fed one of two isoenergic synthetic diets for 7 days; LS (5% energy from cornstarch, 73% energy from corn oil) or HS (71% energy from cornstarch, 7% energy from corn oil), as summarized in Table 1 [19]. The diets contained at least 2.4% corn oil to supply essential fatty acids. The mice were killed by decapitation between 10:00 and 11:00 am. The experimental procedures used in this study met the guidelines of the animal use committee of the University of Shizuoka.

Table 1. Composition of diets

Ingredient	Diet			
	LS		HS	
	Wt. (g)	Energy (%)	Wt. (g)	Energy (%)
Vitamin-free casein	15.9	20.8	15.7	20.9
Cornstarch (β-starch)	3.6	5.5	52.6	70.9
Corn oil	24.7	72.7	2.4	7.2
AIN^{93} Mineral mix	2.8		2.8	
AIN^{93} Vitamin mix	0.8		0.8	
L-cystine	0.24	1.0	0.24	1.0
Choline bitartrate	0.16		0.16	
2% Agar	51.8		25.3	

All values are given in %. Mineral mix and vitamin mix are based on AIN-93 (Oriental Yeast, Tokyo, Japan). Both diets are isoenergic (12.6 kJ/g).

2.2 Preparation of intestinal samples

The entire small intestine was removed and the jejunoileum was divided into three segments of equal length. The proximal third of jejunoileum was flushed twice with ice-cold 0.9% NaCl solution. A 1 cm segment (100 mg) was excised from the middle region of the jejunal loop, and immediately used for RNA extraction. The remaining part of the jejunal loop was used for chromatin immunoprecipitation (ChIP) assays.

2.3 Quantitative RT-PCR

Total RNA was extracted by the acidified guanidine thiocyanate method, as described by Chomczynski and Sacchi [20]. Total RNA samples were stored at −80°C before use in quantitative RT-PCR analysis. The total RNA samples (2.5 μg) were converted into cDNA by reverse transcription using SuperScript™ III reverse transcriptase (Invitrogen, Tokyo, Japan) according to the manufacturer's instructions. To quantitatively estimate the mRNA levels of *Mgam* and TATA box binding protein (*Tbp*), PCR amplification was performed on a Light-Cycler 480 instrument system (Roche, Tokyo, Japan). Real-time PCR reactions were carried out in a total volume of 10 μL containing 400 nM each of gene specific primers, cDNA and SYBR Premix Ex Taq (Takara, Shiga, Japan). The cycle threshold (CT) values of *Mgam* and *Tbp* detected by real-time RT-PCR were converted to signal intensities by the delta–delta method [21], which calculates one CT value as two to the power of the difference between the signal for *Mgam* and the signal for a gene for normalization (*Tbp*). The formula is $[2^{(CT\ Mgam\text{-}CT\ Tbp)}]$. The sequences of the PCR primer pair and the fragment size are listed in Table 2.

Table 2. The sequences of oligonucleotide primers

Gene	Sequence
Mgam mRNA	5′-GCCACCTGGTACGACTATGAA-3′
	5′-TTGTGTGGGAAAGATGTAGCC-3′
Tbp mRNA	5′-CTTCACCAATGACTCCTATGACC-3′
	5′-ACAGCCAAGATTCACGGTAGA-3′
Region on the *Mgam* gene	Sequence
−10 000	5′-CACCAGACTTACTGAAGCAACA-3′
	5′-TCCCAGATCTGTCTGAAGGAA-3′
−2000	5′-TTGAGGGAAGCACCAATACAC-3′
	5′-CCCTCCATTCCTGACTCTTTT-3′
−1000	5′-AAGGGGCAGCTAGACTTCTGTA-3′
	5′-AAAGGAAGTCATGGGACCTGT-3′
0	5′-GGTGGAACAGTAGGCATTTCA-3′
	5′-TCTCTGCCCAGAAATGGTAGA-3′
100 000	5′-GTTTCAAGCCTGCATCCTGTA-3′
	5′-GAATGGGAGGCAGCAATCTAT-3′

2.4 Enzyme assays

Jejunal homogenates in 10 mM potassium-phosphate buffer (pH 7.0) were incubated with 28 mM maltose for 15 min (maltase activity) and with 1% soluble starch for 30 min (glucoamylase activity), as described by Dahlqvist [22]. The reactions were terminated by adding Tris-HCl (pH 8.0) to the final concentration of 100 mM, after which the homogenates were immediately boiled for 3 min to neutralize the enzymes. Concentrations of glucose produced by maltase or glucoamylase in jejunal homogenates were determined by Glucose CII test WAKO (Wako Pure Chemical Industries, Osaka, Japan). Protein was measured according to the method of Lowry *et al.* [23].

2.5 Chromatin immunoprecipitation assay

The mucosa removed from the jejunum was incubated with fixation solution (1% formaldehyde, 4.5 mM Hepes, pH 8.0, 9 mM NaCl, 0.09 mM EDTA, 0.04 mM ethylene glycol tetraacetic acid) in PBS for 30 min at 37°C. The reaction was terminated by the addition of glycine to a final concentration of 150 mM. After being washed in FACS solution (1 × PBS (−), 2% bovine serum, 0.05% NaN_3), the samples were sonicated in SDS lysis buffer (50 mM Tris-HCl, pH 8.0, 10 mM EDTA, pH 8.0, 1% SDS, 0.5 mM phenylmethanesulphonylfluoride) with protease inhibitor tablets (Complete Mini, Roche) (1 tablet/10 mL SDS lysis buffer) when the DNA size of samples was 200–500 bp. The ChIP assay, using 1 μg anti-CDX2 (Bio Genex, CA, USA), anti-HNF1 (Santa Cruz Biotechnology, CA, USA), anti-acetyl-histone H3 (Millipore, Tokyo, Japan), anti-acetyl-histone H4 (Millipore), anti-CREBBP (Santa Cruz Biotechnology), or a control rabbit IgG was performed as described previously [11]. The precipitated DNA was subjected to real-time PCR using primers that corresponded with the indicated sites in the promoter/enhancer and transcription start sites. The CT values of ChIP signals detected by real-time PCR were expressed as the percentage of each ChIP signal for input DNA using the delta–delta method [21]: the CT-value was calculated as two to the power of the difference between the CT-value for a ChIP signal and the CT-value for the input signal. The formula used was $100 \times [2^{(\text{CT IP sample}-\text{CT Input})}]$.

3 Results

3.1 The effects of a HS-diet on jejunal expression of the *Mgam* gene and on maltase and glucoamylase activities

Jejunal expression of the *Mgam* gene was 3.5-fold higher in mice fed the HS-diet than those fed the LS-diet ($p < 0.01$, Fig. 1A). Jejunal maltase (Fig. 1B) and glucoamylase (Fig. 1C) activities were both 3.2-fold higher in mice fed the HS-diet than in those fed the LS-diet ($p < 0.01$).

3.2 The effect of a HS-diet on the binding of CDX2 and HNF1 in the promoter/enhancer regions of the *Mgam* gene

The average of the ChIP signals of normal IgG was 0.011% ± 0.001. The ChIP signals of CDX2 and HNF1 were highly detectable around the transcription start site. ChIP signals of both CDX2 and HNF1 were increased by the HS-diet intake, which was significant at +0 bp for CDX2 and at −2000 bp for HNF1 (Figs. 2A and B).

3.3 The effects of a HS-diet on the acetylation of histones H3 and H4 and on the binding of coactivator CREBBP in the promoter/enhancer and transcriptional regions of the *Mgam* gene

To investigate whether acetylation of histones H3 and H4 on the *Mgam* gene is associated with induction of *Mgam* gene expression by a HS-diet, we performed ChIP assays using antibodies for histone H3 acetylated at lysine 9 and 14, an antibody for histone H3 acetylated at both sites (K9/14) and for histone H4 acetylated at lysine 5, 8, 12 and 16, an antibody detectable for acetylation of histone H3 at these sites (K5/8/12/16) in mice fed a HS- or an LS-diet for 7 days. The ChIP signals of acetylated histone H3 at K9/14 and H4 at K4/8/12/16 in the promoter/enhancer (−10 000, −2000 and −1000 bp) and transcriptional (0 and 10 000 bp) regions of the *Mgam* gene were markedly higher than those of IgG. Acetylation levels of histone H3 at K9/14 gradually increased from the upstream region (−10 000 bp) to the transcriptional region (+10 000 bp) (Fig. 3B), whereas histone H4 was highly acetylated in the promoter/enhancer

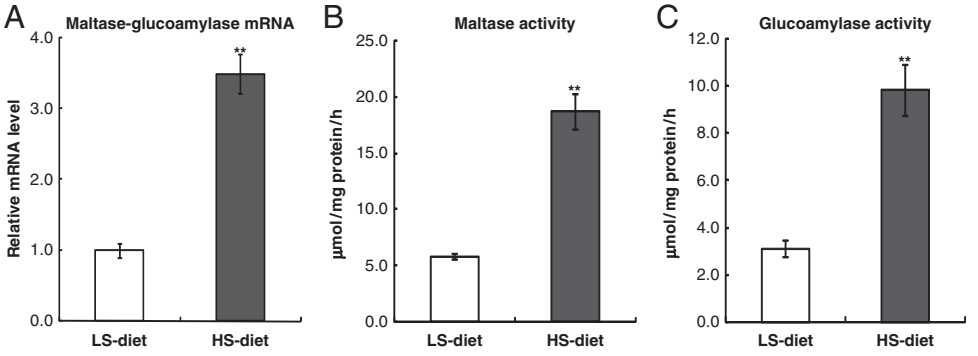

Figure 1. Jejunal expression of the *Mgam* gene (A) and activities of maltase (B) and glucoamylase (C) in mice fed a HS- or LS-diet for 7 days. Means ± SEM of four to seven animals are shown. $^{**}p<0.01$, HS-diet *versus* LS-diet (Student's *t*-test).

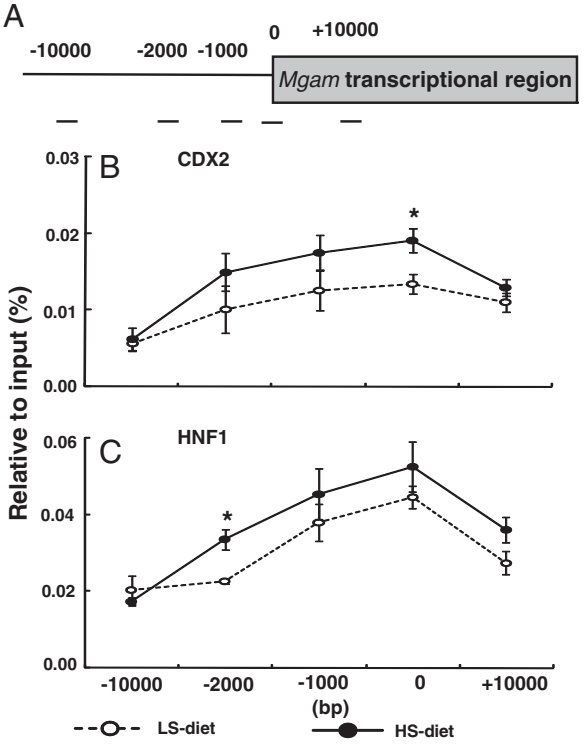

Figure 2. CDX2 and HNF1 binding on the *Mgam* gene in mice fed a HS- or LS-diet for 7 days. (A) Primer pairs used for PCR analysis for ChIP assays. (B) CDX2. (C) HNF1. Means ± SEM of four to seven animals are shown. $^{*}p<0.05$, HS-diet *versus* LS-diet (Student's *t*-test).

region (−2000 and −1000 bp) compared with the transcriptional region (+0 and +10 000 bp) (Fig. 3C). The acetylation of histone H3 at K9/14 was higher in both enhancer/promoter and transcriptional regions in the mice fed the HS-diet compared with those fed the LS-diet (Fig. 3B). The acetylation of histone H4 at K5/8/12/16 was only higher in the enhancer/promoter regions (−10 000 and −2000 bp) of the *Mgam* gene in the mice fed the HS-diet compared with those fed the LS-diet (Fig. 3C).

Because acetylation of histone H3 at K9/14 on the *Mgam* gene was higher and more inducible by the HS-diet than that of histone H4 at K5/8/12/16, we examined the individual signal of lysine 9 (K9) or 14 (K14) of acetylation of histone H3. The ChIP signals using a specific antibody for acetylation levels of histone H3 at K9 gradually increased from −10 000 to −1000 bp and the levels were constantly high in the transcriptional region (+0 bp, +10 000 bp) (Fig. 3D). By contrast, the ChIP signals using a specific antibody for acetylated histone H3 at K14 tended to be higher in the promoter/enhancer region (−2000 and −100 bp) than in the transcriptional region (0 and +10 000 bp) (Fig. 3E). Acetylation of histone H3 at K9 was higher in mice fed a HS-diet than in those fed a LS-diet in all regions of the *Mgam* gene ($p<0.01$), whereas acetylation at K14 was significantly higher in the promoter/enhancer regions (−10 000, −2000 and 1000 bp) in mice fed a HS-diet than those fed a LS-diet (Figs. 3D and E). The ChIP signals for the coactivator CREBBP (generally called CBP) were higher than signals of normal IgG in both groups. The ChIP signals were higher in mice fed a HS-diet than those fed a LS-diet, which was significant at −10 000, −2000, −1000 and +10 000 bp (Fig. 3F).

4 Discussion

In this study we have demonstrated that both jejunal *Mgam* mRNA and maltase and glucoamylase activities were increased by feeding mice a HS-diet. Furthermore, we have demonstrated that CDX2 and HNF1, which are important transcriptional factors for intestinal maturation and *Si* gene expression [11, 13], were bound to the promoter/enhancer regions (−2000 −+0 bp) of the *Mgam* gene, with a peak around +0 bp. This is the first demonstration that CDX2 and HNF1 are bound to the promoter/enhancer region of the *Mgam* gene. The consensus sequences for CDX2 are located on −70 −−66 bp from the translation start site, whereas those for HNF1 are not found in the promoter/enhancer regions (from −2000 to 0 bp) of the *Mgam* gene. The reason may be that consensus sequences for HNF1 are

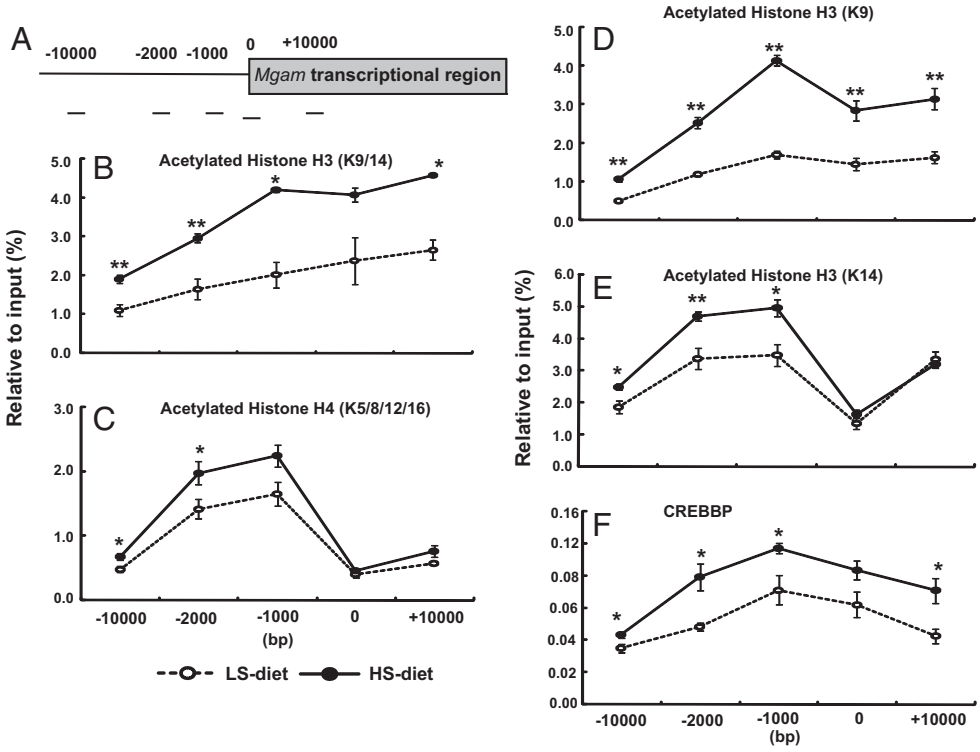

Figure 3. Histone acetylation and CREBBP binding on the *Mgam* gene in mice fed a HS- or LS-diet for 7 days. (A) Primer pairs used for PCR analysis for ChIP assays. (B) Acetylated histone H3 at K9/14. (C) Acetylated histone H4 at K5/8/12/16. (D) Acetylated histone H3 at K9. (E) Acetylated histone H3 at K14. (F) CREBBP. Means ± SEM of four to seven animals are shown. $^{*}p<0.05$, $^{**}p<0.01$, HS-diet *versus* LS-diet (Student's *t*-test).

variable [24]. Previous studies have demonstrated that CDX2 and HNF1 binding sites are located on the promoter region within 200 bp from the transcription initiation site of the mouse *Si* gene [25]. In this study, we have also described that the binding sites for CDX2 and HNF1 on the promoter region of *Mgam* gene are close to the transcription initiation site, since the peak of CDX2 and HNF1 bindings is around the transcription initiation site. These insights indicate that the promoter structures of the *Mgam* and *Si* genes are very similar and this similarity may mean that the expression of these genes is regulated by a HS-diet in a similar way. Further studies using electrophoretic mobility shift assays and reporter assays are needed to investigate which sites in the promoter/enhancer region of the *Mgam* gene are for binding to HNF1 and CDX2. Furthermore, the binding of CDX2 and HNF1 to the promoter/enhancer regions of *Mgam* gene was enhanced by the HS-diet.

These results suggest that induction of the *Mgam* gene by a HS-diet in mice is associated with enhanced binding of CDX2 and HNF1 to the promoter/enhancer region of the *Mgam* gene. Furthermore, we revealed that acetylation of histones H3 and H4 in the promoter/enhancer and transcriptional regions of the *Mgam* gene was enhanced by the HS-diet. Several studies have shown that acetylation of histones H3 (K9/14) and H4 (K5/8/12/16) is associated with the euchromatin region and increases gene expression by recruitment of the transcriptional complex [14–16, 26]. However, it is still unknown which lysine residues of histone H3 have increased acetylation in response to a HS-diet. In this study, we have demonstrated that a HS-diet increases acetylation of histone H3 at K9 in both the promoter/enhancer and the transcriptional regions of the *Mgam* gene and at K14 in the promoter/enhancer region of the *Mgam* gene. Acetylation of histone H3 at K9 was more inducible than at K14 in the promoter/enhancer and transcriptional regions of the *Mgam* gene. Taken together, this shows that the induction of *Mgam* gene expression by a HS-diet is associated not only with binding of CDX2 and HNF1, but also with histone acetylation, particularly of histone H3 at K9. We have previously shown that gene expression of solute carrier family 5, member 1 (*Slc5a1*, generally called SGLT1), which is a transporter for glucose and galactose expressed in the brush border membrane of the small intestine, was enhanced by the HS-diet and the acetylation of histone H3 was increased at K9 rather than at K14 [27]. Thus, the induction of genes related to carbohydrate digestion/absorption by the HS-diet may be regulated strongly by the acetylation of histone H3 at K9, but this hypothesis should be further examined by determining whether a HS-diet affects acetylation at K9 of histone H3 on the *Si* gene.

Furthermore, the binding of CREBBP, which has acetyltransferase activity and a bromodomain that is known to bind to acetylated histones [18], was increased by the HS-diet. This is the first report showing that the binding of one of the coactivators was increased in the promoter/enhancer and transcriptional regions of a jejunal gene by a HS-diet. These results suggest that increased acetylation of histones H3 and H4 may recruit CREBBP in the promoter/enhancer

region of *Mgam* gene, and the recruited CREBBP may subsequently acetylate the histones H3 and H4 in the promoter/enhancer and transcriptional regions of the *Mgam* gene. Further studies are needed to investigate whether other proteins that bind to acetylated histones in the promoter/enhancer and transcriptional regions of the *Mgam* gene, in particular to acetylated histone H3 at K9, are enhanced by a HS-diet.

Recent studies have demonstrated by gene targeting that deficiency of the *Mgam* gene reduces jejunal maltase activity in both heterozygous and homozygous mice and reduces postprandial hyperinsulinemia in homozygous mice, although the inhibition of maltase activity was not complete even in homozygous mice because of the partial maltase activity of sucrase [4, 28]. These results indicate that reduction of *Mgam* gene expression is important for inhibiting postprandial hyperglycemia/hyperinsulinemia and for related diseases such as diabetes. In addition, it is reported that disaccharidase activities, including maltase, were markedly higher in rats with streptozotocin-induced hyperglycemia than in normal rats [29]. Furthermore, a previous study of ours demonstrated that feeding rats a diet containing high-amylose cornstarch, which is more slowly digested in the small intestine than regular corn starch, for 14 days, led to a decrease in disaccharidase activities, including maltase, in the upper jejunum as well as a decrease in serum triacylglycerol [30]. In addition, treating streptozotocin-induced diabetic rats with acarbose, an inhibitor for disaccharidases known to reduce postprandial hyperglycemia, for 12 days led to reduced disaccharidase activities, including maltase, in the jejunum [31]. These results suggest that increased disaccharidase activity is associated with increased lipid abnormality and diabetes, whereas reduced disaccharidase activity caused by drugs or nutrients that decrease the digestion/absorption of carbohydrates, such as acarbose and high-amylose cornstarch, decreases lipid abnormality and diabetes. Further studies are needed to investigate if these changes in disaccharidase activity are regulated at the transcriptional level through binding of transcriptional factors (CDX2, HNF1), a coactivator (CREBBP), or acetylation of histones on their genes.

In conclusion, we have demonstrated for the first time that the induction of *Mgam* gene expression by a HS-diet in mice is regulated not only by transcriptional factors (CDX2 and HNF1), but also by histone acetylation and a coactivator (CREBBP).

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (20590233), a grant from The Naito Foundation and the Global COE program for the Center of Excellence for Innovation in Human Health Sciences, from the Ministry of Education, Science, Sports and Culture of Japan.

The authors have declared no conflict of interest.

5 References

[1] Gray, G. M., Starch digestion and absorption in nonruminants. *J. Nutr.* 1992, *122*, 172–177.

[2] Nichols, B. L., Avery, S., Sen, P., Swallow, D. M. *et al.*, The maltase-glucoamylase gene: common ancestry to sucrase-isomaltase with complementary starch digestion activities. *Proc. Natl. Acad. Sci. USA* 2003, *100*, 1432–1437.

[3] Nichols, B. L., Eldering, J., Avery, S., Hahn, D. *et al.*, Human small intestinal maltase-glucoamylase cDNA cloning. Homology to sucrase-isomaltase. *J. Biol. Chem.* 1998, *273*, 3076–3081.

[4] Quezada-Calvillo, R., Robayo-Torres, C. C., Opekun, A. R., Sen, P. *et al.*, Contribution of mucosal maltase-glucoamylase activities to mouse small intestinal starch α-glucogenesis. *J. Nutr.* 2007, *137*, 1725–1733.

[5] Goda, T., Koldovsky, O., Dietary regulation of small intestinal disaccharidases. *World Rev. Nutr. Diet.* 1988, *57*, 275–329.

[6] Goda, T., Suruga, K., Komori, A., Kuranuki, S. *et al.*, Effects of miglitol, an α-glucosidase inhibitor, on glycaemic status and histopathological changes in islets in non-obese, non-insulin-dependent diabetic Goto-Kakizaki rats. *Br. J. Nutr.* 2007, *98*, 702–710.

[7] Yamamoto, M., Otsuki, M., Effect of inhibition of α-glucosidase on age-related glucose intolerance and pancreatic atrophy in rats. *Metabolism* 2006, *55*, 533–540.

[8] Bustamante, S. A., Goda, T., Koldovsky, O., Dietary regulation of intestinal glucohydrolases in adult rats: comparison of the effect of solid and liquid diets containing glucose polymers, starch, or sucrose. *Am. J. Clin. Nutr.* 1986, *43*, 891–897.

[9] Goda, T., Yamada, K., Bustamante, S., Koldovsky, O., Dietary-induced rapid decrease of microvillar carbohydrase activity in rat jejunoileum. *Am. J. Physiol.* 1983, *245*, G418–G423.

[10] Goda, T., Regulation of the expression of carbohydrate digestion/absorption-related genes. *Br. J. Nutr.* 2000, *84*, S245–S248.

[11] Honma, K., Mochizuki, K., Goda, T., Carbohydrate/fat ratio in the diet alters histone acetylation on the sucrase-isomaltase gene and its expression in mouse small intestine. *Biochem. Biophys. Res. Commun.* 2007, *357*, 1124–1129.

[12] Tanaka, T., Suzuki, A., Kuranuki, S., Mochizuki, K. *et al.*, Higher expression of jejunal LPH gene in rats fed the high-carbohydrate/low-fat diet compared with those fed the low-carbohydrate/high-fat diet is associated with *in vitro* binding of Cdx-2 in nuclear proteins to its promoter regions. *Life Sci.* 2008, *83*, 122–127.

[13] Boudreau, F., Rings, E. H., van Wering, H. M., Kim, R. K. *et al.*, Hepatocyte nuclear factor-1 α, GATA-4, and caudal related homeodomain protein Cdx2 interact functionally to modulate intestinal gene transcription. Implication for the developmental regulation of the sucrase-isomaltase gene. *J. Biol. Chem.* 2002, *277*, 31909–31917.

[14] Schubeler, D., MacAlpine, D. M., Scalzo, D., Wirbelauer, C. *et al.*, The histone modification pattern of active genes

revealed through genome-wide chromatin analysis of a higher eukaryote. *Genes Dev.* 2004, *18*, 1263–1271.

[15] Roh, T. Y., Cuddapah, S., Zhao, K., Active chromatin domains are defined by acetylation islands revealed by genome-wide mapping. *Genes Dev.* 2005, *19*, 542–552.

[16] Soutoglou, E., Talianidis, I., Coordination of PIC assembly and chromatin remodeling during differentiation-induced gene activation. *Science* 2002, *295*, 1901–1904.

[17] Goda, T., Takase, S., Hosoya, N., Hydrolysis of α-D-glucopyranosyl-1,6-sorbitol and α-D-glucopyranosyl-1,6-mannitol by rat intestinal disaccharidases. *J. Nutr. Sci. Vitaminol. (Tokyo)* 1988, *34*, 131–140.

[18] Chan, H. M., La Thangue, N. B., p300/CBP proteins: HATs for transcriptional bridges and scaffolds. *J. Cell. Sci.* 2001, *114*, 2363–2373.

[19] Goda, T., Takase, S., Dietary carbohydrate and fat independently modulate disaccharidase activities in rat jejunum. *J. Nutr.* 1994, *124*, 2233–2239.

[20] Chomczynski, P., Sacchi, N., Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal. Biochem.* 1987, *162*, 156–159.

[21] Livak, K. J., Schmittgen, T. D., Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods* 2001, *25*, 402–408.

[22] Dahlqvist, A., Assay of intestinal disaccharidases. *Anal. Biochem.* 1968, *22*, 99–107.

[23] Lowry, O. H., Rosebrough, N. J., Farr, A. L., Randall, R. J., Protein measurement with the Folin phenol reagent. *J. Biol. Chem.* 1951, *193*, 265–275.

[24] Krasinski, S. D., Van Wering, H. M., Tannemaat, M. R., Grand, R. J., Differential activation of intestinal gene promoters: functional interactions between GATA-5 and HNF-1 α. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2001, *281*, G69–G84.

[25] Traber, P. G., Silberg, D. G., Intestine-specific gene transcription. *Annu. Rev. Physiol.* 1996, *58*, 275–297.

[26] Roh, T. Y., Ngau, W. C., Cui, K., Landsman, D., Zhao, K., High-resolution genome-wide mapping of histone modifications. *Nat. Biotechnol.* 2004, *22*, 1013–1016.

[27] Honma, K., Mochizuki, K., Goda, T., Inductions of histone H3 acetylation at lysine 9 on SGLT1 gene and its expression by feeding mice a high carbohydrate/fat ratio diet. *Nutrition* 2009, *25*, 40–44.

[28] Nichols, B. L., Quezada-Calvillo, R., Robayo-Torres, C. C., Ao, Z. *et al.*, Mucosal maltase-glucoamylase plays a crucial role in starch digestion and prandial glucose homeostasis of mice. *J. Nutr.* 2009, *139*, 684–690.

[29] Schedl, H. P., Al-Jurf, A. S., Wilson, H. D., Elevated intestinal disaccharidase activity in the streptozotocin-diabetic rat is independent of enteral feeding. *Diabetes* 1983, *32*, 265–270.

[30] Goda, T., Urakawa, T., Watanabe, M., Takase, S., Effect of high-amylose starch on carbohydrate digestive capability and lipogenesis in epididymal adipose tissue and liver of rats. *J. Nutr. Biochem.* 1994, *5*, 256–260.

[31] Goda, T., Yamada, K., Sugiyama, M., Moriuchi, S., Hosoya, N., Effect of sucrose and Acarbose feeding on the development of streptozotocin-induced diabetes in the rat. *J. Nutr. Sci. Vitaminol. (Tokyo)* 1982, *28*, 41–56.

