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Effect of fructose or sucrose feeding with different levels on oral glucose tolerance test in normal and type 2 diabetic rats*

Sanghee Kwon, You Jin Kim and Mi Kyung Kim§

Department of Food and Nutritional Sciences, Ewha Womans University, 11-1 Daehyung-dong, Seodaemun-gu, Seoul 120-750, Korea

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Abstract

This study was designed to determine whether acute fructose or sucrose administration at different levels (0.05 g/kg, 0.1 g/kg or 0.4 g/kg body weight) might affect oral glucose tolerance test (OGTT) in normal and type 2 diabetic rats. In OGTT, there were no significant differences in glucose responses between acute fructose- and sucrose-administered groups. However, in normal rats, the AUCs of the blood glucose response for the fructose-administered groups tended to be lower than those of the control and sucrose-administered groups. The AUCs of the lower levels fructose- or sucrose-administered groups tended to be smaller than those of higher levels fructose- or sucrose-administered groups. In type 2 diabetic rats, only the AUC of the lowest level of fructose-administered (0.05 g/kg body weight) group was slightly smaller than that of the control group. The AUCs of fructose-administered groups tended to be smaller than those of the sucrose-administered groups, and the AUCs of lower levels fructose-administered groups tended to be smaller than those fed higher levels of fructose. We concluded from this experiment that fructose has tendency to be more effective in blood glucose regulation than sucrose, and moreover, that smaller amount of fructose is preferred to larger amount. Specifically, our experiments indicated that the fructose level of 0.05 g/kg body weight as dietary supplement was the most effective amount for blood glucose regulation from the pool of 0.05 g/kg, 0.1 g/kg and 0.4 g/kg body weights. Therefore, our results suggest the use of fructose as the substitute sweetener for sucrose, which may be beneficial for blood glucose regulation.

Key Words: Fructose, sucrose, oral glucose tolerance test

Introduction

The dietary habit of Koreans has changed progressively to one that resembles that of people in the Western world (The Korean Nutrition Society, 2006) and this has caused an increase in the consumption of sucrose. According to the food balance sheet provided by the "Korean Rural Economic Institute" (2004), the average amount of sucrose supplied for each Korean adult was 4.8 g per day in 1962 and has increased to 57 g per day in 2004. Although it is still relatively small compared with that of the USA, the production and consumption are still increasing (The Korean Nutrition Society, 2006). Type 2 diabetes is increasing at epidemic rates in the USA (Mokdad *et al*., 1999; Mokdad *et al*., 2000; Mokdad *et al*., 2001) and in the developing countries including China (Pan *et al*., 1997) and India (Ramachandran *et al*., 1997). From 1935 to 1996, the prevalence of diagnosed type 2 diabetes climbed nearly 765% (Centers for Disease Control and Prevention NCfHS, Division of Health Interview Statistics, 1997). The global figures are predicted to rise 46% from 150 million cases in 2000 to 221 million in 2010 (Zimmet *et al*., 2001). The incidence of type 2 diabetes is also at an epidemic level in Korea and is increasing. For example, the incidence of diabetes for those aged 30 years or older has increased from 6.6% in 1998 to 8.1% in 2005 (Ministry of Health and Welfare, 1999; Ministry of Health and Welfare, 2006). Epidemiological studies have identified a significant positive correlation between dietary sucrose intake and the incidence of diabetes (Basciano *et al*., 2005). We suspect that this steady increase in sucrose consumption in Korea will contribute to the increase of diabetes (Basciano *et al*., 2005), so there is an urgent need for the selection and application of appropriate substitute sweeteners.

Fructose is believed to be more slowly absorbed from the gastrointestinal tract than glucose. When disaccharides such as sucrose or maltose enter the intestine, they are cleaved by disaccharidases. A sodium-glucose cotransporter absorbs glucose that is formed from the cleavage of sucrose. In contrast, fructose has no active absorption mechanism in the intestinal mucosa but is slowly and incompletely absorbed by facilitated diffusion (Bray *et al*., 2004; Uusitupa, 1994). Because of this slow absorption, the blood glucose-increasing effect of fructose is lower than after ingestion of most other carbohydrate sources

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§ **Corresponding Author:** Mi Kyung Kim, Tel. 82-2-3277-3092, Fax. 82-2-3277-2862, Email. mkk@ewha.ac.kr

(Bantle *et al*., 1983; Cannon *et al*., 1986; Crapo & Kolterman, 1984; Henry *et al*., 1991; Jeckins *et al*., 1981; Swan *et al*., 1966). After absorption, glucose and fructose enter the portal circulation and are transported to the liver, where fructose can be taken up and converted to glucose, or pass into the general circulation (Bray *et al*., 2004). Fructose is metabolized mainly by the liver and to a lesser extent by the kidney and intestinal mucosa (Ludwig *et al*., 1999; Truswell, 1992). Fructose transepithelial transport in intestine is initiated at the apical side by GLUT 5 and GLUT 2, and is thought to be released through the basolateral membrane by GLUT 2 (Kellett & Brot-Laroche, 2005). In the metabolism of fructose, the first reaction is catalyzed by fructokinase, an enzyme that is not dependent on insulin. Fructose does not stimulate insulin secretion from pancreatic β cells. The lack of stimulation by fructose is likely because of the low concentrations of the fructose transporter GLUT5 in β cells (Basciano *et al*., 2005; Bray *et al*., 2004; Curry, 1983; Mayer, 1993; Sato *et al*., 1996; Uusitupa, 1994). In contrast to sucrose and glucose, some nutritionists regard fructose as a relatively safe form of sugar. Because it does not require insulin for uptake into cells, moderate fructose intake does not affect blood glucose levels adversely, at least in the short term (Bantle *et al*., 1986). Glycemic index (GI) is a system of classifying carbohydrate-containing foods according to how fast they are digested and absorbed during the postprandial period. The GI has a value of 100 for glucose and baked potato, 19 for fructose and 68 for sucrose (Truswell, 1992). A related concept, glycemic load (GL), also takes into consideration the amount of carbohydrates in portion of food (Ciok & Dolna, 2006). Glycemic Index (GI) and Glycemic Load (GL) play a pivotal role in carbohydrate classification and for food choice by diabetic patients. Postprandial glycemic response and insulinemia are strongly related to the values of GI and GL (Pankowska *et al*., 2006). Several recent studies have suggested that consuming low GI and GL diet may be associated with a lower risk for type 2 diabetes (Salmeron *et al*., 1997a; 1997b; 1997c). In addition, fructose is sweeter than sucrose. In sweetness comparative studies, when sucrose is set at a scale of 100, fructose is 173 and glucose is 74 (Schauberger, 1977). For these reasons, it has been proposed as a useful energy source and a substitute for sucrose in the diet for patients with diabetes (Bantle, 1989; Koivisto, 1978; Nutrition Subcommittee of the British Diabetic Association's Professional Advisory Committee, 1990; Olefsky & Crapo, 1980). However, diets specifically high in fructose have been shown to contribute to metabolic disturbances in animal models resulting in weight gain, hyperlipidemia and hypertension (Hwang *et al*., 1987; Kasim-Karakas *et al*., 1996).

Some studies examining the effects of fructose consumption on blood glucose regulation have shown conflicting results (Jurgens *et al*., 2005). The optimal dose of fructose compared with sucrose has not been well evaluated. The metabolic consequence of fructose, compared with sucrose, needs to be examined in experimental animals and human with normal or type 2 diabetes (Olefsky & Crapo, 1980). Therefore, this study was designed to determine whether the supplement of different levels of fructose or sucrose might affect blood glucose regulation in Sprague-Dawley (SD) and Goto-Kakizaki (GK) rats with type 2 diabetes, respectively. The goal was to determine the effect of fructose, compared with sucrose, on glucose tolerance, as dietary supplements.

Materials and Methods

Animals and Diets

Seventy male SD rats of nine-month old [Slc (SD), Outbred, Charles River Origin, Japan SLC, Inc] were placed in individual stainless steel wire-mesh cages in a room with 12:12 h light-dark cycle, temperature of 22-24℃ and a relative humidity of 45 ± 5%. The rats were fed with a normal diet for the first seven days of adaptation. The diet was formulated according to the nutrient content of the 93M diet of the American Institute of Nutrition (AIN) (Portha *et al*., 1991). Cornstarch (Dyets Inc., USA) was included as a source of carbohydrate, soybean oil (CJ Co., Korea) was included as a source of lipid and casein (Dyets Inc., USA) was included as a source of protein. Mineral and vitamin mixtures, prepared in accordance with the 1993 recommendation of the AIN, were purchased from Dyets, Inc., USA. SD rats weighed 632 ± 15 g at the end of the adaptation period. They were then stratified according to body weight and allocated randomly into seven groups for the experimental period.

Seventy male GK rats of six-week old [GK/Slc, Inbred, Tohoku University School of Medicine, Japan SLC, Inc] were placed in individual stainless steel wire-mesh cages in a room with 12:12 hr light-dark cycle, temperature of 22-24℃ and relative humidity of 45 ± 5%. The rats were fed with a normal diet for the first seven days of the adaptation period. The diets of GK rats were formulated according to the nutrient content of the 93G diet of the AIN (Portha *et al*., 1991). The GK rat is a spontaneous diabetic animal model of non-insulin-dependent diabetes mellitus, which is characterized by progressive loss of β-cells in the pancreatic islets with fibrosis. This model was produced by repeated selective breeding of rats with glucose intolerance starting from a nondiabetic Wistar rat colony. The characteristics of the GK rat include mild hyperglycemia at fasting, impaired glucose tolerance on glucose load and impaired secretion of insulin in response to glucose in vivo (Hasegawa *et al*., 2001; Koyama *et al*., 1998; Ostenson *et al*., 1993; Ostenson, 1996). The GK rats weighed 132 ± 5 g at the end of the adaptation period. The rats were then stratified according to body weight and blocked randomly into seven groups for the experimental period.

This study was conducted at the nutrition laboratory of Ewha Womans University in compliance with the Guide for the Care and Use of Laboratory Animals (Ostenson *et al*., 1993). The rats were allowed free access to the experimental diets and deionized water during the experimental period. Body weights were

recorded once a week. For determination of food intake, the amount of food offered was weighed and the weights of any orts were recorded three times per week.

Oral glucose tolerance test

The design of experiments is shown in Table 1. In the experiment, different levels of fructose (Crystalline fructose 99.5%, Kato Kaguku Co., Japan) or sucrose (Daesang Co, Korea) were administered to normal SD and type 2 diabetic GK rats as supplements to test their effects on blood glucose regulation using the OGGT.

After the rats had fasted for 12 h, a 50% glucose solution (1 g/kg of body weight) with the supplement of fructose or sucrose at different levels (0.05 g/kg, 0.1 g/kg or 0.4 g/kg body weight) was orally administered, and blood was taken from the tail vein at 0 (before the solution load), 30, 60, 90 and 120 min afterward (The Korean Society of Food Science and Nutrition, 2000). Blood glucose concentrations were determined immediately using an Accu-chek (Roche Diagnostics, Germany). According to studies on the OGTT in which glucose solution is added with fructose, the typical amount of fructose added is about 10% (w/w) of the glucose solution. Moreover, adding a smaller proportion of fructose was shown to be more effective in observing the regulating effect on blood glucose than adding a larger amount (Moore *et al*., 2000). For these reasons, we set the fructose amount to be added to the glucose solution to 5% and 10% (w/w) of the glucose solution in this study. These amounts correspond to 0.05 g and 0.1 g per kg of body weight, respectively, for the glucose solution at 1 g per kg of body weight. For completeness, we also tested the case in which the added fructose amount was greater than 10% (w/w) of the glucose solution. In this case, fructose was 0.4 g per kg of body weight derived from the intake of added sugar, which is the equivalent of 19.1 g per day for a normal 60 kg adult Korean (Dietary Reference Intakes for Koreans, 2005). The increment in blood glucose after the glucose load was expressed in terms of AUC from the time when the fasting blood was drawn until 120 min postload blood sampling. AUC was calculated by *WinNolin* program (version 1.1, Pharsight Co., USA).

Statistical Analysis

All statistical analyses were performed by the SAS program package version 9.1. All results were expressed as the mean ± standard error (SE). The data were analyzed by one-way analysis of variance (ANOVA) and differences between experimental groups were evaluated using Duncan's multiple range tests at the $p<0.05$ significance level.

Results

Oral glucose tolerance in normal rats

Daily food intake and body weight change per week in SD rats were not significantly different among any groups. In this study, the range of daily food intake and body weight change per week were 29.85~33.36 g/day and 3.79~4.55 g/day, respectively. The OGTT results for SD rats are shown in Fig. 1. There was no significant difference in the glucose response between the acute fructose and sucrose administered groups. At 30 min and 60 min after solution ingestion, although there were no significant differences between treatments, blood glucose concentrations of rats administered the 0.1F or 0.4F diets tended to be lower than those of the rats administered the 0.1S or 0.4S levels, respectively. At 90 min and 120 min after solution ingestion, the blood glucose concentrations of the fructose-administered groups tended to be lower than those of the sucrose-administered groups at matching concentration. Supplement of fructose to the glucose load tended to reduce the glycemic response to the OGTT.

The AUC data of the glucose response in SD rats is shown in Fig. 2. There was no significant difference in the AUC of the glucose response between acute fructose- and sucrose-

Table 1. Experimental design of the Study

Group[1)]	Adaptation period (7 days)	Load solutions used in oral glucose tolerance tests (all in g/kg body weight)
C	Normal diet	Glucose 1
0.05S		Glucose 1 + Sucrose 0.05
0.1S		Glucose 1 + Sucrose 0.1
0.4S		Glucose 1 + Sucrose 0.4
0.05F		Glucose 1 + Fructose 0.05
0.1F		Glucose 1 + Fructose 0.1
0.4F		Glucose 1 + Fructose 0.4

[1)] C: Control group; OGTT (glucose 1 g/kg body weight)
0.05S: Sucrose administration group; OGTT+S (0.05 g/kg body weight)
0.1S: Sucrose administration group; OGTT+S (0.1 g/kg body weight)
0.4S: Sucrose administration group; OGTT+S (0.4 g/kg body weight)
0.05F: Fructose administration group; OGTT+F (0.05 g/kg body weight)
0.1F: Fructose administration group; OGTT+F (0.1 g/kg body weight)
0.4F: Fructose administration group; OGTT+F (0.4 g/kg body weight)

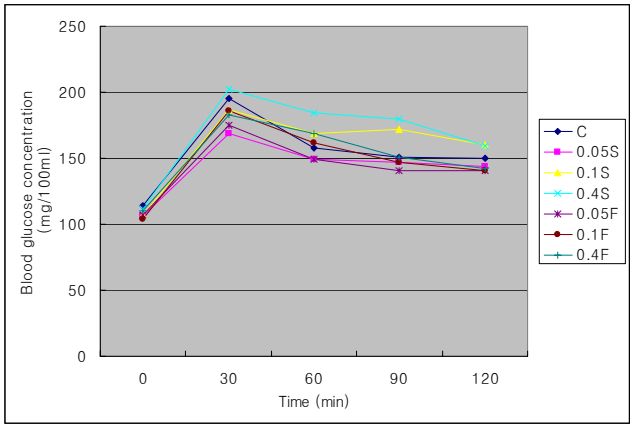

Fig. 1. The changes in blood glucose concentration during an oral glucose tolerance test in SD rats

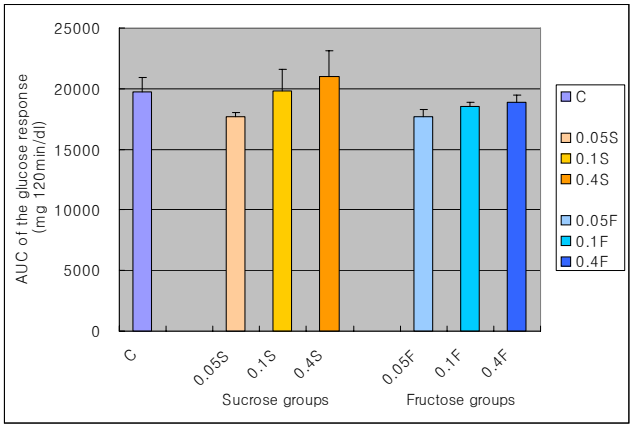

Fig. 2. The areas under the curve of the glucose response in SD rats

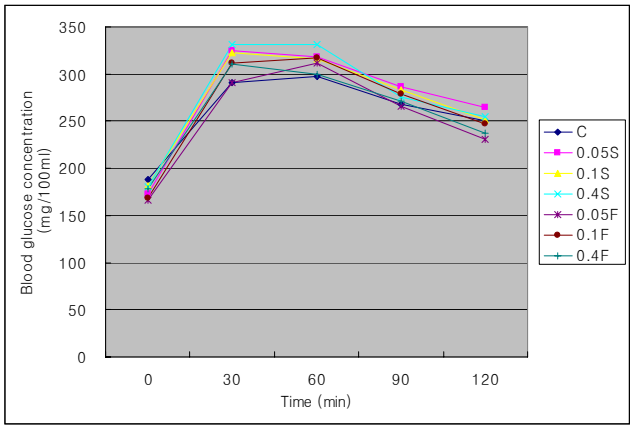

Fig. 3. The changes of blood glucose concentration during oral glucose tolerance test in GK rats

administered groups, whereas the AUCs of fructose-administered groups tended to be smaller than those of control or sucrose-administered groups at matching concentration. The AUCs of lower-level fructose- or sucrose-administered groups tended to be smaller than those of groups administered higher levels of fructose or sucrose at matching concentration. The AUCs of the 0.05F, 0.1F, 0.4F and 0.05S groups tended to be smaller than that of the control group, and the AUC of the 0.05F group was the smallest. The AUCs of fructose-administered groups tended to be smaller than those of the sucrose-administered groups. The AUC of the glucose response, calculated as the change from basal values in each group, was about 0.01% smaller with the 0.05F diet than with the 0.05S diet. It was 7% smaller with the 0.1F diet than with the 0.1S diet and 10% smaller with the 0.4F diet than with the 0.4S diet. The AUC of the glucose response was about 10% smaller with the 0.05F diet than with the control diet. The supplement of fructose to the glucose load tended to improve glucose tolerance in these SD rats.

Oral glucose tolerance in diabetic rats

Daily food intake and body weight change per week in GK rats were not significantly different among any groups. In this study, the range of daily food intake and body weight change per week was 14.67~15.59 g/day and 4.59~5.19 g/day, respectively. The OGTT data for GK rats are shown in Fig. 3. There was no significant difference in the glucose response between the acute fructose- and sucrose-administered groups. At 30 min after solution ingestion, blood glucose concentrations of the sucrose-administered groups were higher than those of the fructose-administered groups. At 60, 90 and 120 min after solution ingestion, blood glucose concentrations of the fructose-administered groups tended to be lower than those of sucrose-administered groups at matching concentration, except for the 0.1F and 0.1S groups at 60 min. At 30 and 60 min, the blood glucose concentrations of the control group tended to be lower than those of the experimental groups. At 90 and 120 min, the blood glucose

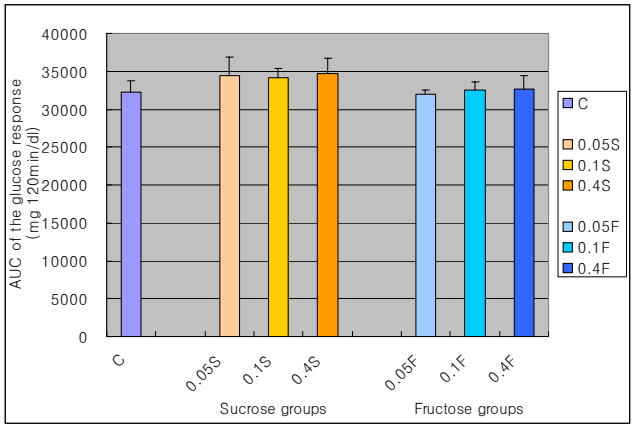

Fig. 4. The areas under the curve of the glucose response in GK rats

concentration of the 0.05F group tended to be lower than those of the other groups. Supplement of fructose to the glucose load, compared with supplement of sucrose to the glucose load, tended to reduce the glycemic response to the OGTT. In contrast to data for normal animals, diabetic rats should be higher blood glucose level during the first 120 min after 12 hr of fasting than normal rats. Furthermore, while the blood glucose level of normal rats was peaked at around after 30 min from 12 hr of fasting, that of diabetic rats was peaked after 30 min to 60 min from 12 hr of fasting.

The AUCs of the glucose response in GK rats are shown in Fig. 4. There were no significant differences between the acute fructose- and sucrose-administered groups, whereas the AUCs of fructose-administered groups tended to be smaller than those of the control or sucrose-administered groups at matching concentration. The AUCs of higher-level fructose- or sucrose-administered groups tended to be larger than those of rats administered lower-level fructose or sucrose diets, except for the 0.05S and 0.1S groups. Only the AUC of the 0.05F administered group tended to be smaller than that of the control group. The AUC was the smallest in the 0.05F group, followed by the

control, 0.1F, 0.4F and sucrose-administered groups. The AUC of glucose response, calculated as the change from basal values in each group, was approximately 7% smaller with the 0.05F diet than with the 0.05S diet, 6% smaller with the 0.1F diet than with the 0.1S diet, and 6% smaller with the 0.4F diet than with the 0.4S diet. The AUC of the glucose response was about 0.7% smaller with the 0.05F diet than with the control diet. Consequently, the AUCs of fructose-administered groups tended to be smaller than those in the sucrose-administered groups, and the AUCs of the lowest-level fructose-administered groups were the smallest. In conclusion, the supplement of a small amount of fructose to a glucose load, compared with supplement of a small amount of sucrose to a glucose load, tended to improve glucose tolerance in GK rats with type 2 diabetes.

Discussion

In this study, different levels of fructose or sucrose were administered to normal SD and type 2 diabetic GK rats as supplements to test their effects on blood glucose regulation, using the OGTT. The present study implies that the addition of fructose seems more attributive to blood glucose regulation regardless of the added amount in comparison with sucrose administration. Moreover, in our present study where we conducted adding three different amounts of fructose, the results imply that smaller amount of added fructose induces more effective blood glucose regulation while not significantly. Had fructose been added more consistently over a period of time, as opposed to just once as done in this study, a clearer effect of fructose administration in blood glucose regulation might have been observed in agreement with the known results in the literature. Furthermore, we also expect to observe a more definitive result had we used mid-aged rats that have difficulty in blood glucose regulation as opposed to young rats as done in this study. In the future, more extensive experiments regarding the blood glucose regulation need be explored. The fact that supplemental fructose contributing to blood glucose regulation can be explained from metabolic adaptation-in other words, the ability to suppress endogenous glucose production during hyperglycemia and increased net hepatic glucose uptake and metabolism in normal subjects. There are various studies on the effect of supplement of fructose or sucrose to blood glucose in OGTTs in which fructose or sucrose was added to the glucose load in normal subjects. Moore *et al*. (2000) examined the effect of fructose on glucose tolerance in 11 normal human volunteers. Each volunteer underwent an OGTT that consisted of 75 g of glucose with or without 7.5 g of fructose on two separate experiments at least one week apart. The OGTT with fructose in comparison with that without fructose showed significantly smaller AUC of the change in plasma glucose ($p<0.05$). Low-dose fructose improves the glycemic response to an oral glucose load in normal adults without significantly enhancing the insulin or triglyceride responses. The increase in the arterial blood glucose concentration during fructose infusion was only half as great as it was in the absence of fructose (Shiota *et al*., 2002). In that study, the increased glycolytic flux associated with the inclusion of fructose was probably secondary to an increase in the intracellular glucose 6-phosphate content. This in general is secondary to the activation of glucokinase, perhaps with an associated increase in the activity of phosphofructokinase (Shiota *et al*., 2002). A small proportion of ingested fructose generally improves glycemic control because it increases net hepatic glucose uptake via enhanced translocation of glucokinase, increased hepatic glycogen synthesis and hepatic glycolysis (Petersen *et al*., 2001). Increased amount of added fructose resulted in a reduced blood glucose regulating effect. The fact that an increased supplement of fructose translates to extra calories, which transform to glucose and eventually to a higher blood glucose level, can account for this (Faeh *et al*., 2005). If fructose intake is very high, or if it leads to excessive energy consumption, it can have an adverse effect on glucose regulation (Levi & Werman, 1998).

There have been studies on the effects of supplement with fructose or sucrose on the blood glucose level during OGTTs in diabetic subjects. In the present study, we observed that the AUC of only the 0.05F group tended to be smaller than that of the control group. The blood glucose regulations of sucrose-administered groups tended to be poorer than those of the fructose-administered groups. Unlike the normal animals, higher fructose supplement in the diabetic rats had adverse effects on blood glucose regulation compared with control group. For diabetic animals, insulin secretion becomes uncontrollable after an intake of high amount of sugar, and the ability to suppress endogenous glucose production during hyperglycemia becomes impaired. These experimental results suggest that higher doses of fructose increase the blood glucose level and that only small doses of fructose will have beneficial effects on blood glucose regulation in diabetic subjects. Moore *et al*. (2001) studied five adults with type 2 diabetes who underwent an OGTT that consisted of 75 g of glucose with or without 7.5 g of fructose on two separate experiments that took place at least one week apart. The subjects with type 2 diabetes demonstrated a 14% reduction in the AUC of the glucose response to an OGTT when a small dose of fructose was added to the glucose load. The improvement in glucose tolerance with fructose ingestion in this study did not occur at the expense of increased insulin secretion. Wolf *et al*. (2002) evaluated the effects of supplemental fructose on postprandial glycemia in an animal model. After overnight food deprivation, Zucker fatty (fa/fa) rats were given a meal glucose tolerance test. At a dose of 0.16 g/kg body weight, fructose reduced the AUC by 34% when supplemented to a glucose challenge (1 g/kg). In a dose-response study (0.1, 0.2 and 0.5 g/kg body weight), supplemental fructose reduced the peak rise in plasma glucose ($p<0.01$). A low dose of fructose (0.075 g/kg body) reduced ($p<0.05$) the AUC by 18%. These

findings have great clinical potential for the prevention of postprandial hyperglycemia in people with diabetes. Atkinson *et al* (2000) reported that supplemental fructose (1, 2 and 4 g/kg body weight) reduced ($p<0.05$) the early (10 min) postprandial plasma glucose concentrations after a glucose challenge. However, the incremental AUC for plasma glucose was unaffected.

The mechanism by which a small dose of fructose can decrease the blood glucose level in normal rats may be explained as follows. When glucose and fructose are supplemented together, they compete for GLUT2 which exists in the apical surface so that fructose is induced to suppress the absorption of glucose. Recently, Kellett and Brot-Laroche (2005) have discovered a new pathway of sugar absorption, the apical GLUT2 pathway. GLUT2 is an attractive candidate as the dominant sugar transporter because it is a high-capacity transporter, has a much higher Km for glucose and fructose, and transports both substrates (Kellet & Brot-Laroche, 2005; Kwon *et al*., 2007). In the classical model, GLUT2 has an exclusively basolateral location. But, more recent localization data showed that GLUT2 localizes to the apical surface. Binding sites on GLUT2 for fructose and glucose are the same (Corpe *et al*., 1996; Kellett & Helliwell, 2000). Higher blood glucose level and less effective blood glucose regulation were observed when we performed OGTT to diabetic rats than to normal rats. This can be accounted for by the impaired insulin secretion which leads to reduced translocation of GLUT4 in diabetic rats. The latter is associated with decreased glucose transport in type 2 diabetic rats (Watson & Pessin, 2001; Wood & Trayhum, 2003). Increased supplement with fructose translates to extra calories, which in turn transforms to glucose. Eventually, these higher blood glucose levels can account for this reduced regulation.

We concluded from this experiment that fructose has tendency to be more effective in blood glucose regulation than sucrose, and moreover, that smaller amount of fructose is preferred to larger amount. Specifically, our experiments indicated that the fructose level of 0.05 g/kg body weight as dietary supplement was the most effective amount for blood glucose regulation from the pool of 0.05 g/kg, 0.1 g/kg and 0.4 g/kg body weights. Therefore, our results suggest the use of fructose as the substitute sweetener for sucrose, which may be beneficial for blood glucose regulation.

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