



Letter

Transient increase in plasma urate induced by a single oral dose of fructose in rats

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ABSTRACT — Hyperuricemia, an elevated urate concentration in blood, is the precursor state of gout and is associated with metabolic syndrome and chronic kidney disease. The increasing prevalence of hyperuricemia in recent years is thought to be due to environmental factors, particularly diet. Here, we investigated whether and how fructose induces an increase in plasma urate concentration using a rat model. Oral administration of fructose increased plasma urate concentration within 15–30 min, without an increase in urate excretion into urine or gastrointestinal tract, and this action was evident at a dose of 7.5 g/kg b.w. On the other hand, the same dose of glucose did not elicit a hyperuricemic effect at all, and thus the effect is thought to be a specific property of fructose. The absence of an increase in urinary or gastrointestinal excretion suggested that the increase did not result from an increase in urate production. Instead, a decrease in urate clearance could have a potential to explain the increase in plasma urate concentration. In conclusion, the present study characterized the time course and dose response of a fructose-induced increase in plasma urate concentration using a rat model.

Key words: Fructose, Hyperuricemia, Gout, Urate

INTRODUCTION

Uric acid is the end product of purine metabolism in humans and is present in the blood as urate. Hyperuricemia is the precursor state of gout and its incidence has increased substantially in recent years (So and Thorens, 2010) in parallel with the rising prevalence of gout (Wallace *et al.*, 2004). Hyperuricemia is also associated with chronic kidney diseases (Zhu *et al.*, 2014) and metabolic syndrome (Sui *et al.*, 2008) and has thus become a serious public concern. The recent increase in hyperuricemia is thought to be related to environmental factors, such as diet and lifestyle. Among these factors, sugars and sweet-

eners are of particular interest because they represent the largest single source of calories in the diets of developed countries such as the United States of America (Wells and Buzby, 2008), and epidemiological studies have revealed a clear association between sugar-sweetened beverages and hyperuricemia (Choi *et al.*, 2008; Bombardieri *et al.*, 2010; Zgaga *et al.*, 2012). It is, however, not clear which ingredients in sugar-sweetened beverages are responsible for the hyperuricemic effect.

Fructose is the primary sweetener in sugar-sweetened beverages, and it is estimated that its consumption is increasing (Wells and Buzby, 2008). Since current food-labelling practices do not provide information on fructose

content (Walker *et al.*, 2014; Ministry of Health, Labour and Welfare, Japan 2019, 2020), the potential relationship between hyperuricemia and the level of fructose consumption has been assessed based on interviews or questionnaires about food consumption. One such assessment in U.S. individuals revealed a positive association between hyperuricemia and fructose consumption (Choi *et al.*, 2008), whereas another study in Scottish individuals found no such association (Zgaga *et al.*, 2012). Possible explanations for this discrepancy are differences in the study populations, levels of fructose consumption, and the methods used to estimate consumption. A more valid approach for determining the conditions under which fructose increases serum urate would be an examination of the effects of fructose administration on serum urate concentration in a controlled animal-experiment.

Hyperuricemia is classified into overproduction and/or underexcretion types based on renal urate excretion and urate clearance (Boss and Seegmiller, 1979). In addition to the renal excretion pathway, urate is excreted via extra-renal excretion pathways, such as through intestinal excretion (Burns and Wortmann, 2011). The importance of the intestinal excretion of urate has been elucidated in recent studies; genetic ablation of a urate exporter decreased intestinal excretion of urate and increased serum urate concentrations in mice (Hosomi *et al.*, 2012; Ichida *et al.*, 2012). In addition, a decrease in intestinal excretion is estimated to be a common cause of hyperuricemia in humans (Ichida *et al.*, 2012; Matsuo *et al.*, 2013). However, it has not yet been explored whether intestinal excretion plays a role in fructose-induced hyperuricemia. In the present study, we developed a rat model of fructose-induced hyperuricemia in order to discover the conditions under which oral administration of fructose increases serum urate. Following this, we examined the dynamic aspects of fructose-induced hyperuricemia, including the urinary and intestinal excretion of urate.

MATERIALS AND METHODS

Animals and treatment

All animal experiments were performed using approved animal protocols (P13-41) and guidelines established by the committee of animal experiments of the School of Pharmacy of the Tokyo University of Pharmacy and Life Sciences. Male Sprague-Dawley rats (180–200 g in weight) and Wistar rats (200–220 g in weight) were obtained from Japan SLC, Inc. (Shizuoka, Japan) and kept in an animal room at a temperature of $23 \pm 1^\circ\text{C}$, at a humidity of $50 \pm 10\%$, with a 12-hr/12-hr light–dark cycle (lights on at 7:00). Laboratory rodent powder diet

(CE-2; CLEA Japan, Inc., Tokyo, Japan) supplemented with 2% potassium oxonate (Tokyo Chemical Industry, Tokyo, Japan) and distilled water were provided *ad libitum*. Fructose, glucose, or water at a volume of 10 mL/kg was administered by gavage.

Collection of blood and urine

Blood was obtained from the tail veins of rats, and was immediately centrifuged to separate plasma. The plasma specimens were stored at -80°C until analysis. We closely adhered to this procedure, since our preliminary examination revealed that urate concentration could be increased depending on the time-span between blood collection and freezing.

Urine was collected for 4 hr using metabolic cages (3701M081, Tecniplast Japan, Tokyo, Japan).

Intestinal closed loop experiment

Rats were deeply anesthetized with pentobarbital sodium (50 mg/kg body weight *i.p.*, Dainippon Sumitomo Pharma, Osaka, Japan). Intestinal closed loops were made using approximately 10 cm of ileum. PBS was injected into each intestinal loop. After 4 hr, the loops were collected to analyse the contents. Urate excretion into the intestinal loop was calculated from the following equation: (urate excretion to the loop) = (urate concentration in the loop) \times (intestinal loop volume) / (length of the intestinal loop).

Biochemical assays

Urate concentration was determined by QuantiChrom Uric Acid Assay Kit (Bioassay Systems, California, USA). Multiple assays for plasma specimens revealed that the reproducibility of the assays was above 95%, as coefficient of variation for intra- and inter-assays were 2.4% and 1.8% under the conditions of the present study. Creatinine concentration in urine was determined by colorimetric assay based on Jaffe's reaction (#500701, Cayman Chemical, Michigan, USA).

Renal clearance

Renal clearances of creatinine and urate were determined using urine specimens collected in a metabolic cage for 4 hr and plasma specimens collected just before and after the metabolic cage experiment. Creatinine concentration was measured using Creatinine Fluorometric Assay Kit (#K625-100, BioVision, California, USA). Concentrations in plasma and urine specimens derived from each rat were determined in the same assay to avoid possible inter-assay deviations. Clearance (Cr), urinary urate excretion (UUE), and fractional excretion of urate

Fructose-induced hyperuricemia in rats

clearance (FEUA) were calculated by the following equations: $Cr = UUE / (\text{average plasma concentrations of creatinine at 0 and 4 hr})$; $UUE = (\text{urinary urate concentration}) \times (\text{urine volume for 4 hr})$; and $FEUA = (\text{urate clearance}) / (\text{creatinine clearance})$, respectively.

Statistical analyses

Analysis of the data was carried out with JMP statistical software (SAS Institute, North Carolina, USA). All data are expressed as the mean \pm SEM. For the analyses of time course experiments, plasma urate concentration values of rats in a group were subtracted with the mean values on the starting timepoint of the group, and thus the starting timepoint also had SEM. Differences in the means were analyzed by one-way analysis of variance (ANOVA) followed by post hoc tests with Dunnett's method. Differences were considered significant at $p < 0.05$.

RESULTS

To develop a rat model of fructose-induced hyperuricemia, Sprague-Dawley rats were treated with potassium oxonate, an inhibitor of uricase, a urate metabolizing enzyme which has been lost in humans (Kratzer *et al.*, 2014). Plasma urate concentration increased in rats fed 2.0% (w/w) potassium oxonate for a week (3.62 ± 0.26 mg/dL vs. 2.07 ± 0.13 mg/dL). Oral administration of fructose at a dose of 7.5 g/kg b.w. to the oxonate-treated rats significantly increased plasma urate at 15 and 30 min post-administration (Fig. 1A). In contrast, oral administration of glucose (7.5 g/kg b.w.) or vehicle (water) did not increase plasma urate. The cumulative increase in plasma urate after 4 hr was estimated (Fig. 1B) by calculating the area under the curve (AUC) of urate in the time-course experiments (Fig. 1A). The lowest values in the fructose group exceeded the highest values in the glucose and water groups, indicating that oral administration of fructose to Sprague-Dawley rats induces an increase in plasma urate for at least 4 hr. In order to examine the reproducibility and universality of these results, another time-course experiment was conducted using oxonate-treated rats of a different strain, the Wistar rat. The experiment using Wistar rats produced essentially the same results (Fig. 1C) as the Sprague-Dawley rat experiment (Fig. 1A); plasma urate concentration began to increase at 15 min and were significantly higher at 30 min compared to initial levels (0 min). These results demonstrated that fructose has the ability to increase plasma urate in our rat model of humanized urate metabolism.

Oxonate-treated Sprague-Dawley rats were orally administered fructose at a dose of 0, 0.8, 2.5, or 7.5 g/kg b.w.

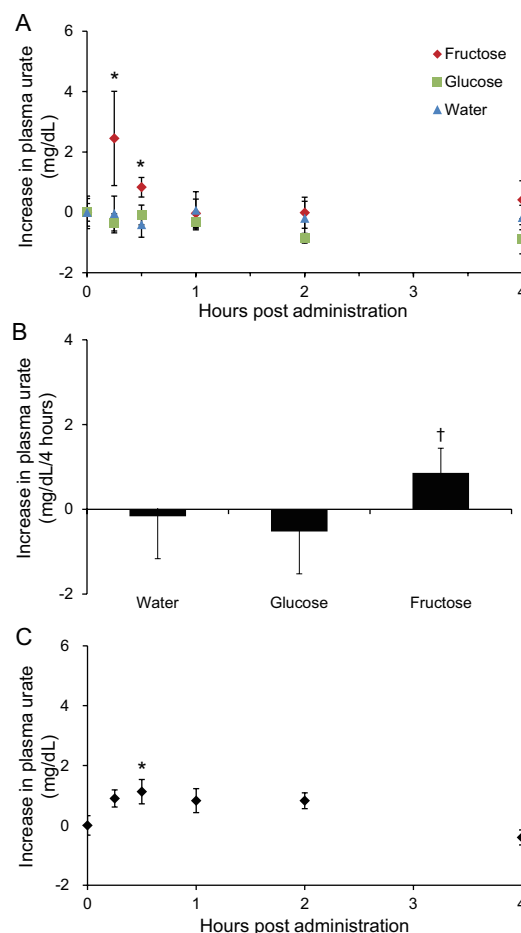


Fig. 1. Time-courses of plasma urate changes after fructose ingestion in rats. (A) Increase in plasma urate concentration in male Sprague-Dawley rats ($n = 8$) administered 7.5 g/kg body weight of fructose, glucose, or vehicle (water), measured at the time points indicated. (B) Cumulative increases in plasma urate concentration over 4 hr calculated from AUCs of the time-course experiments. (C) Time-course experiment in Wistar rats. Increase in plasma urate concentration in male Wistar rats ($n = 5$) administered 7.5 g/kg body weight of fructose, measured at the time points indicated. *Significant difference vs. 0 hr. †Significant difference vs. glucose group.

for 15 min. A significant increase and a non-significant increase in plasma urate were observed in rats treated with fructose at doses of 7.5 and 2.5 g/kg b.w., respectively (Fig. 2). No increase was observed in rats administered fructose at a dose of 0.8 or 0 g/kg b.w. Doses higher than 7.5 g/kg b.w. could not be administered with a gastric tube and syringe owing to technical difficulties.

To investigate the mechanisms of the fructose-induced

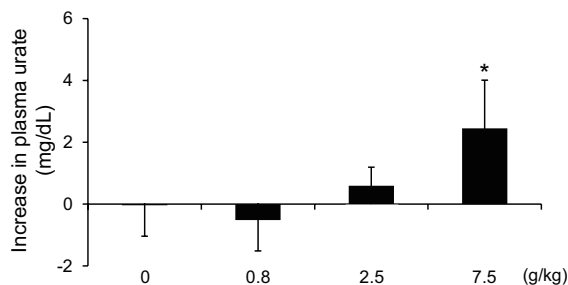


Fig. 2. Dose-response of fructose-induced hyperuricemia. Increase in the plasma urate concentration of male Sprague-Dawley rats ($n = 7-8$) 15 min after administration of the indicated doses of fructose (0, 0.2, 2.5, or 7.5 g/kg body weight) by gavage.

increase in plasma urate, we examined two major routes of urate excretion: renal and gut excretions (Hosomi *et al.*, 2012; Ichida *et al.*, 2012). We first evaluated the amount of urate excreted into urine, or UUE, for 4 hr. The UUE in Sprague-Dawley rats administered fructose at a dose of 7.5 g/kg b.w. was not statistically different from that of rats administered the same dose of glucose or water (Fig. 3A). Another indicator, the ratio of urate to creatinine concentrations in urine, which is not confounded by urine volume or osmolality, tended to be lower in fructose-treated rats than in glucose- and water-treated rats (Fig. 3B). For the evaluation of intestinal urate excretion, we determined the amount of urate excreted into the ileum for 4 hr in oxonate-treated Sprague-Dawley rats, since urate excretion into the gut is greater in the ileum than in the jejunum or colon (Hosomi *et al.*, 2012). The amounts of urate excreted into the ileum were not different among rats treated with 7.5 g/kg fructose, glucose, or water (Fig. 3C).

We next examined the balance of the renal urate excretion and plasma urate concentration. To this end, we determined the renal urate clearance and the ratio of this to creatinine clearance (FEUA), since creatinine is minimally regulated by reabsorption or secretion in the kidney. Urate clearance tended to be reduced in rats administered fructose compared to that in rats administered glucose and water, although there was no significant difference (Fig. 4A). The FEUA in the fructose group tended to be lower compared to that in the control groups (Fig. 4B), although this was also not significant.

DISCUSSION

The present study was conducted to clarify conditions under which the oral intake of fructose increases plasma urate concentration and the mechanism of fructose-induced

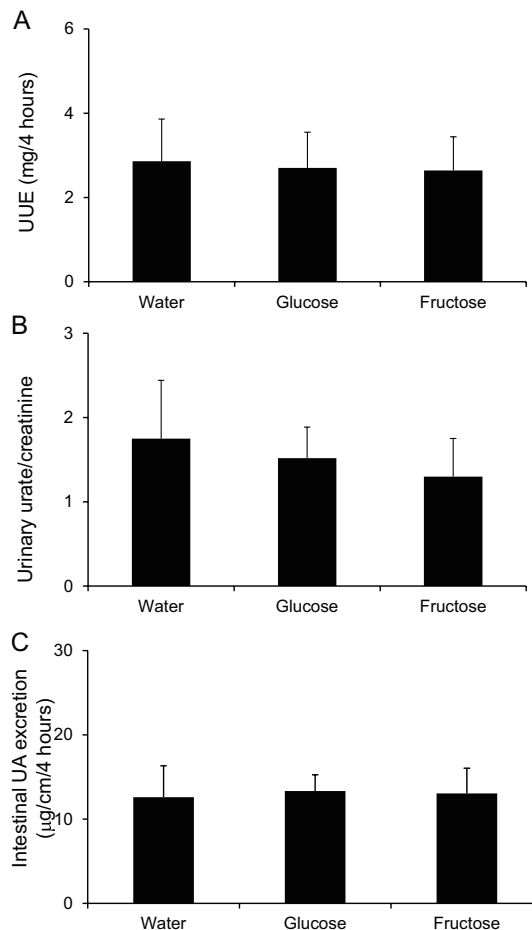


Fig. 3. Urate excretion in fructose-administered rats. (A) UA excretion into urine (UUE) over 4 hr and (B) urinary urate concentration normalized by urinary creatinine concentration in male Sprague-Dawley rats ($n = 5-6$) administered 7.5 g/kg body weight fructose, glucose, or vehicle. (C) Intestinal urate excretion in fructose-treated rats. UA excretion into the intestinal ileum over 4 hr in male Sprague-Dawley rats ($n = 4-5$) administered 7.5 g/kg body weight fructose, glucose, or vehicle.

hyperuricemia. To this end, a rat model of humanized urate metabolism, oxonate-treated rats, was used. We demonstrated that a single administration of fructose increased plasma urate over a short time span of 15–30 min. This action of fructose was evident at a dose of 7.5 g/kg b.w. but was less clear at 2.5 g/kg b.w. Plasma urate concentrations increased by 2.45 and 0.83 mg/dL at 15 and 30 min post-administration of fructose, respectively, and the cumulative increase in plasma urate over 4 hr was estimated to be 0.86 mg/dL. Importantly, the same dose of glucose did not elicit a hyperuricemic effect at all, and thus the effect is thought to be a specific characteristic of fructose.

Fructose-induced hyperuricemia in rats

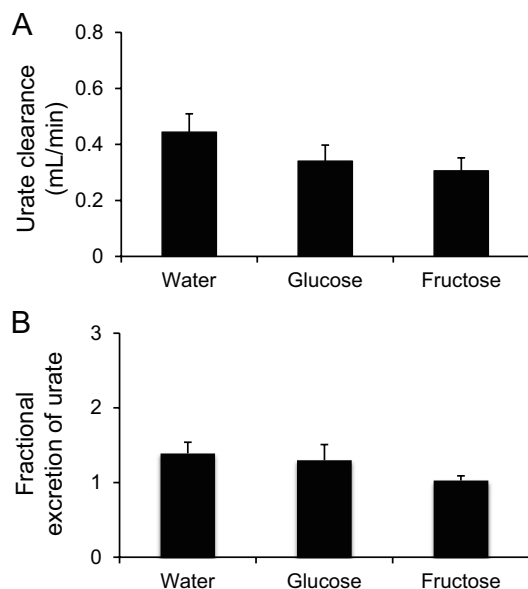


Fig. 4. Renal clearance of urate in fructose-treated rats. (A) Urate clearance, (B) FEUA in male Sprague-Dawley rats 4 hr after administration of 7.5 g/kg body weight fructose (n = 10), glucose (n = 8), or vehicle (n = 7).

The theoretical causes of hyperuricemia are an increase in urate production and/or a decrease in urate clearance (Burns and Wortmann, 2011). Increased UUE is an indicator of an increase in urate production, as increased urate in blood results in increased urate excretion out of the body. In our rat model of fructose-induced hyperuricemia, both UUE and intestinal urate excretion were not increased at all. On the other hand, the urinary urate clearance itself and the associated indicators (FEUA, UUE, and the ratio of urate to creatinine) tended to decrease following fructose administration. The reason for the non-significance of the decrease in urate excretion indicators in our rat experiments might involve incomplete inhibition of uricase by oxonate with resultant degradation of some urate into allantoin. Of note, humans are devoid of uricase (Kratzer *et al.*, 2014) and thus blood urate is not further metabolized, making humans more sensitive to alterations in urate excretion than rats. Based on the present results, the potential increase in urate production induced by fructose is not large enough to increase urate excretion over 4 hr and thus an increase in urate production is not thought to be a major mechanism of hyperuricemia induced by a single oral dose of fructose at least under the conditions of the present study. Instead, a decrease in urinary urate clearance is thought to have the potential to be the mechanism behind fructose-induced hyperuricemia. However, there exists a limitation in the estimation of urate clearance in

our study; the intestinal loop method might influence on the absorption process of fructose in the digestive track. Further investigation into the mechanisms of fructose-induced increases in urate using a refined rat model with more extensively humanized urate metabolism in which uricase activity is completely lost by genetic ablation would help to clarify the cause of fructose-induced hyperuricemia.

There have been a few other studies reported in which a single oral administration of fructose resulted in an increase in plasma urate in rats (Stavric *et al.*, 1976; Moreno and Hong, 2012; Kaneko *et al.*, 2017). These studies, however, lack information on the peak period of the urate increase and the dose-response relationship, and so the present study is the first to reveal the time course and dose response of a fructose-induced increase in plasma urate in rats. In one of these studies, Kaneko *et al.* (2017) reported that fructose administration resulted in significant decrease in intestinal urate excretion 12–20 hr post administration. This mechanism could not account for the fructose-induced hyperuricemia in the short time observed in our rat model, but might contribute to delayed hyperuricemia after intake of fructose. A few other studies have reported that fructose did not induce an increase in plasma urate in rats (Itoh, 1983; Niewoehner *et al.*, 1984). A potential factor contributing to the increase in plasma urate appears to be a fructose dose > 5 g/kg b.w. Strain differences in rats could also contribute to differences in the observed fructose-induced increase in plasma urate; oxonate-treated Wistar rats showed a prolonged and smaller peak increase in plasma urate after fructose administration compared to Sprague-Dawley rats under our experimental conditions.

Fructose-induced hyperuricemia has also been reported in humans. While a relatively low dose of fructose does not increase serum urate (Lecoultré *et al.*, 2013), larger doses of fructose (approximately 1 g/kg b.w. and above) do induce hyperuricemia (Stirpe *et al.*, 1970; Dalbeth *et al.*, 2013, 2014a, 2014b). The overall characteristics of fructose-induced hyperuricemia, such as peak period (15–30 min) and degree of urate increase (approximately 1 mg/dL), in oxonate-treated rats were found to be similar to those in humans, with a slight difference in the doses of fructose required (> 5 g/kg b.w. in rats vs. approximately 1 g/kg b.w. in humans). Of note, it has recently been reported that fructose-induced hyperuricemia in human subjects was not accompanied by an increase in UUE (Lecoultré *et al.*, 2013). Such a refractory regulation of UUE in fructose-induced hyperuricemia was also observed in our rat study. Thus, oxonate-treated rats could complement human studies and be a useful model for invasive analyses of fructose-induced hyperuricemia, including the analysis of urate metabolism in the liver and urate excre-

tion into the intestine.

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Conflict of interest---- The authors declare that there is no conflict of interest.

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