Pre-Exercise Glucose Ingestion May Improve Endurance Capacity in East Asian Student Athletes with Lower Blood Glucose Response

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Summary The main purpose of this study was to investigate the influence of pre-exercise glucose ingestion after a 2.5-h fast on the endurance capacity and blood glucose response in East Asian athletes who is expected to have genetically low insulin response. A total of 8 Japanese student athletes ingested 1.5 g/kg body mass of glucose (G trial) or 0.5 g/kg body mass of artificial sweetener dissolved in water (P trial) 30 min before exercise test after consuming a standardized breakfast. The exercise test comprised 40 min cycling exercise at 50% maximal oxygen uptake (V̇O₂max), immediately followed by cycling to exhaustion at 70% V̇O₂max. Before analyzing the data, we grouped the subjects into two groups depending on whether they showed rapid increase in blood glucose at the onset of exercise (increase rate in LOW group is <20% and HIGH group is ≥20%) to evaluate subject’s insulin response to glucose feeding. No subjects developed rebound hypoglycemia (<70 mg/dL) in the G trial of both group. Significantly higher blood glucose during exercise was recognized only in the G trial of LOW group. Although no significant difference was observed between the two trials of both group, cycling time to exhaustion in the LOW group tended to increase because of glucose ingestion. These results suggest that pre-exercise ingestion of glucose in East Asian student athletes does not induce rebound hypoglycemia regardless of difference in individual insulin responses. Furthermore, individuals with low insulin responses seem to improve endurance performance with glucose ingestion before exercise.

Key Words exhaustion, rebound hypoglycemia, Japanese, breakfast, substrate oxidation

Carbohydrates (CHO) are an essential energy source for prolonged exercise. Development of muscle fatigue during prolonged exercise is caused by a decrease in blood glucose levels late during exercise when muscle and liver glycogen contents are low (1). Therefore, CHO supplementation during exercise has a positive effect on the endurance capacity by supplying additional energy substrate in the form of blood glucose late during exercise (1, 2). However, the effects of CHO ingestion 30–60 min before exercise (pre-exercise) on endurance capacity are still debatable because there are previous studies reporting positive (3, 4), negative (5, 6), or no effect (7–10).

Significant amount of insulin is released from pancreas almost instantly when CHO is ingested (11). Insulin activates a signaling pathway in muscles and promotes GLUT-4 protein to move to the muscle cell membrane, which facilitates glucose uptake in muscles (11). As a result, glycolytic pathway and CHO oxidation is activated (12). On the other hand, fat oxidation in muscle cell is suppressed (13) because insulin has a potential to inhibit lipolysis; thus, it reduces the availability of free fatty acid (FFA) (14). Therefore, when CHO is ingested before exercise, dependence on muscle glycogen for energy production during exercise increases, which in turn accelerates muscle glycogenolysis (15, 16). Additionally, combination of hyperinsulinemia induced by CHO ingestion and exercise-induced GLUT-4 protein translocation can cause a rapid decrease in blood glucose termed as “rebound hypoglycemia,” early during exercise (5, 7, 9, 11, 15–24). These combined metabolic responses might explain why pre-exercise CHO ingestion does not always have a positive effect on endurance capacity (24).

Previous work has shown that rebound hypoglycemia and reduced fat utilization are mediated, in part, by hyperinsulinemia (21). Based on this report, the East Asian population (the Japanese, Chinese, and Korean population) is unlikely to be affected by the negative metabolic responses of pre-exercise CHO ingestion because their insulin secretory capacity is genetically lower (insulin sensitivity is higher) than that of the Western population (25, 26). Therefore, pre-exercise CHO ingestion in East Asian athletes might not reduce but improve the endurance capacity for exercise by supplying an additional energy substrate. However, only few studies have investigated the effect of pre-exercise CHO ingestion in East Asians. Kondo et al. (27) investigated the influence of pre-exercise glucose ingestion in a Japanese population, but they did not measure endurance performance. In the study carried out by Okano et al. (28),

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the subjects ingested fructose in order to prevent hyper-insulinemia. Thus, the effect of pre-exercise glucose ingestion on endurance capacity remains unknown. In addition, prolonged fasting has been shown to be disadvantageous for athletes (29); many studies have investigated the effect of pre-exercise CHO ingestion on endurance capacity, except two studies (5, 28), in which their subjects fasted for 6–14 h before onset of exercise (3, 4, 7–10, 18–21, 23, 24). This experimental design does not appropriately reflect the actual competitive situation. Therefore, the purpose of this study was to examine the effect of pre-exercise glucose ingestion on metabolic responses and endurance capacity in a fed state in Japanese student athletes.

MATERIALS AND METHODS

Subjects and pre-experimental protocol. A total of 8 healthy Japanese males were recruited from university sports clubs. Before the experiment, each subject performed an incremental cycling test (75XLIII; COMBI Wellness, Tokyo, Japan) until volitional exhaustion to determine the maximal oxygen uptake ($V\cdot O_{2\text{max}}$) (AE-310S; Minato Medical Science, Osaka, Japan). Their body weight, body fat, skeletal muscle percentage (“Karada Scan” HBF-362; Omron, Kyoto, Japan), and fasting blood glucose levels (Glutest Neo Alpha; Sanwa Scientific Laboratory, Aichi, Japan) were also measured. All subjects completed a questionnaire of food frequency (“Excel Eiyo-kun” Food frequency questionnaire based on food groups, ver. 5; Kenpakusha, Tokyo, Japan) to determine their state of nutrient intake. Their physical characteristics are shown in Table 1. All subjects were divided into two groups so as not to show significant difference in each measurement item measured in pre-experiment between the groups. All subjects provided written informed consent after the experimental purpose and protocols were explained. This study was approved by the Ethics Committee on Human Experimentation of Faculty of Human Science, Kanazawa University (approval number 2018-13) and is registered with the University Hospital Medical Information Network in Japan, number UMIN000035067. This investigation was conducted according to the Declaration of Helsinki.

Experimental design. This study was performed as a single-blind crossover study. Each subject participated in two trials and were asked to fast for 12 h before each trial day. They were also asked to refrain from exercise before each trial day and to abstain from ergogenic aids, such as protein, creatine, or branched chain amino acids, during the experimental period. The two experimental trials were separated by 1 wk on the basis of previous studies (27, 28). In both trials, subjects consumed a standardized dinner containing 824 kcal (15.4% protein energy ratio, 21.0% fat energy ratio, 63.6% CHO energy ratio) 12 h before reporting to the laboratory. A standardized breakfast containing 713 kcal (13.0% protein energy ratio, 22.5% fat energy ratio, 64.5% CHO energy ratio) was ingested 180 min before the exercise test.

Exercise protocol. The exercise protocol is shown in Fig. 1. To avoid the influence of circadian rhythm on blood glucose and insulin secretion, the exercise test was performed in the morning, and the starting time of the exercise test was standardized for each subject. Sub-
Subjects reported to the laboratory (temperature: $23.7\pm 0.6^\circ$C, humidity: $57.1\pm 8.3\%$) 185 min before exercise test after an overnight fast. Body weight and composition (fat and skeletal muscle percentage) was measured. Next, they consumed a breakfast 180 min before the exercise test and rested quietly for 130 min. At 30 min before exercise test, their blood glucose was measured and then they consumed either a beverage including 1.5 g/kg body mass of glucose (G trial) or 0.5 g/kg body mass of artificial sweeteners (Pal Sweet Calorie Zero; Ajinomoto, Tokyo, Japan) (P trial). The amount of CHO was established in reference to recommended intakes for pre-competition (30). Subjects were then assessed for their condition according to an interview sheet, and their critical flicker frequency (CFF; T.K.K. flicker meter, type I; Takei Scientific Instruments, Niigata, Japan) was measured to assess central fatigue. “Study of fatigue feelings” (Jikaku-sho shirabe), a questionnaire produced by the Research Group of Industrial Fatigue part of the Japan Society for Occupational Health, was also measured to assess for any unusual fatigue feelings using the visual analog scale (31). This questionnaire consists of 25 items of subjective fatigue grouped into five factors: Group I, sleepiness; Group II, unstable feeling; Group III, unpleasantness; Group IV, tiredness; Group V, blurriness. A higher score indicates greater fatigue (32). At 15 min before exercise test, their blood glucose was measured again and they consumed water to avoid dehydration. After a 3-min warm-up cycling workload of 40 W, subjects pedaled at a frequency of 50–60 rpm at 50% $\dot{V}O_{2\text{max}}$ for 40 min. After that, the workload was raised to a level corresponding to 70% $\dot{V}O_{2\text{max}}$ and subjects continued cycling until exhaustion, defined as the point of inability to maintain 50 rpm. During exercise, blood glucose, expired gas, and rate of perceived exertion (RPE) using Borg’s scale were measured. CHO and fat oxidation rates were measured from expired gas. Oxidation rates were calculated based on a prior study (33) assuming that protein oxidation during exercise was negligible. If the calculated value was less than 0, the oxidation rate was considered to be zero. After exercise, CFF and “Study of fatigue feelings” were measured in the sitting state.

Data analysis and statistical analysis. We considered blood glucose levels <70 mg/dL as hypoglycemia, in accordance with prior work (27). The subjects were grouped into two groups depending on whether they showed rapid increase in blood glucose at the onset of exercise due to glucose feeding (increase rate in LOW group is <20% and HIGH group is $\geq$20%). All statistical analyses were performed using IBM SPSS statistics 25 (Advanced Analytics, Inc., Tokyo, Japan). A repeated measures analysis of variance on two factors (group-time) was used to examine blood glucose, CHO and fat oxidation rates, and variations of RPE. When a significant interaction was revealed, a Bonferroni post-hoc test was conducted. Differences in mean values between the G trial and the P trial were tested by a Wilcoxon signed-rank test. All data are presented as mean±SD. Significance was set at $p<0.05$.

RESULTS

Blood glucose levels

In the LOW and HIGH group, the blood glucose levels in the G trial decreased from a peak value (LOW group, $112\pm 6$ mg/dL; HIGH group, $123\pm 6$ mg/dL) at the onset of exercise to a basal value (LOW group, $97\pm 12$ mg/dL; HIGH group, $85\pm 11$ mg/dL) at 20 min after the start of exercise (Fig. 2A, B). It but did not reach the mean values below 70 mg/dL in the both group. Furthermore, none of the subjects in the both group developed rebound hypoglycemia by glucose feeding.

There was a significant main effect of the trial in the LOW group ($p<0.05$), which indicated that the blood glucose levels during exercise in the G trial was significantly higher than that in the P trial (Fig. 2A). However, blood glucose levels during exercise in the HIGH group were similar in the two trials (Fig. 2B).

Substrate oxidation

In the LOW and HIGH group, CHO oxidation rates were similar between the G and P trial (Fig. 3A, B). While fat oxidation rates in the LOW group were similar in the two trials (Fig. 3C), a significant main effect of trial was recognized in the HIGH group ($p<0.05$, Fig. 3D). This result indicates that fat oxidation rates during exercise in the G trial was significantly lower than that in the P trial (Fig. 3D).

Exercise performance time in cycling at 70% $\dot{V}O_{2\text{max}}$

In the HIGH group, no significant difference was observed in time to exhaustion between the G and P trial (G trial, 737±376 s vs P trial, 768±398 s; Fig.
Effect of Pre-Exercise Glucose Ingestion

Meanwhile in the LOW group time to exhaustion were approximately 33.8% longer than in the P trial, although there was no significant difference between the two trials (G trial, 830 ± 198 s vs P trial, 620 ± 102 s; Fig. 4A).

Fatigue evaluation

Amount of variations of CFF are shown in Fig. 5A and B. Values are presented as data of pre-exercise values minus that of post-exercise values. Although no significant difference was recognized between the G and P trial in the LOW and HIGH group (Fig. 5A, B), values in the LOW group shows a tendency to increase in the G trial compared with the P trial (Fig. 5A).

Amount of variations of RPE during exercise are shown in Fig. 6A and B. Values are presented as data minus the value of 0 min after the start of exercise.
from that of each measurement point. Although there is no significant interaction effect between trials and measurement times in the LOW and HIGH group (Fig. 6A, B), in the HIGH group the variation of RPE first during exercise in the G trial was higher than that in the P trial (Fig. 6B).

Amount variations of “Study of fatigue feelings” are shown in Fig. 7A and B. Values are presented as data of pre-exercise values minus that of post-exercise values. In the LOW group, there is no significant difference between the G and P trial (Fig. 7A). However, in the HIGH group the fatigue categories of Group III of “Study of fatigue feelings” was significantly higher than that in the P trial (p<0.05, Fig. 7B).

Comparison of LOW group and HIGH group under each trial of each measurement item

There was no significant difference between the LOW and HIGH group under each trial of each measurement item (Data not shown).

**DISCUSSION**

This study was the first to examine the effect of pre-exercise glucose ingestion on metabolic responses and endurance capacity in East Asian student athletes.

Rebound hypoglycemia is caused as a result of the combined effects of hyperinsulinemia and exercise on the uptake of glucose by the active tissues (15). It has been reported that individual with high insulin response is more prone to develop rebound hypoglycemia in the fasting condition (27). Therefore, we evaluated the subject’s insulin response to glucose feeding even though this study was performed in the fed (breakfast) condition. Because we could not measure insulin concentration, we grouped the subjects into two groups depending on whether they showed rapid increase in blood glucose levels after glucose feeding. Insulin concentration rises as blood glucose level increases; thus, it is plausible that insulin secretion of subjects who showed a rapid rise in blood glucose level by glucose feeding is higher than that of subjects who did not show it.

In this study, the subjects with the highest and lowest weight ingested approximately 100 g and 75 g glucose, respectively, 30 min before exercise. It is well known that when CHO (50–100 g) is ingested 30–60 min before exercise, rebound hypoglycemia can occur early during exercise in Western population (5, 7, 9, 15–24). However, none of the subjects developed rebound hypoglycemia in the LOW and HIGH group. Exercise intensi-
ties and insulin sensitivities of individuals do not affect occurrence of rebound hypoglycemia (17, 20), which might be explained by the genetic characteristics of East Asians of having lower insulin secretory capacity (25). In fact, insulinogenic index, which is an index of early phase (first 30 min during OGTT) insulin secretion, in Japanese is about three-fold less than the Western population (34). Foster et al. (5) have reported that blood glucose levels significantly decreased from approximately 120 mg/dL at the onset of exercise to nearly hypoglycemic levels (70 mg/dL) at 10 min after the start of exercise when 75 g glucose was ingested 30 min before exercise. Although in this study the blood glucose levels (123 ± 6 mg/dL) at the onset of exercise in the HIGH group is almost consistent with the previous study (5), the blood glucose levels during exercise did not fall below 80 mg/dL, i.e., the mean lowest value. These results reflect a low insulin secretory capacity of East Asian. Therefore, it is assumed that insulin-dependent glucose uptake at the onset of exercise was suppressed and rebound hypoglycemia did not occur. However, Kondo et al. (27) conducted a research on Japanese male students and found that some subjects had rebound hypoglycemia by pre-exercise glucose ingestion. This discrepancy between studies could also be explained by a difference of insulin levels at the onset of exercise. In this study, subjects consumed a solution of 1.5 g/kg body mass of glucose (approximately 75–100 g), but those in the previous study (27) consumed a beverage of 150 g of glucose. Subsequently, they demonstrated ingestion of 150 g glucose raised pre-exercise insulin levels, and this response was more than two-fold compared with the response to 75 g of glucose (27). Based on this, we suspect that at the onset of exercise the insulin levels of the subjects in our study were lower than those of subjects in the previous study, which suggests that our glucose dosage did not cause rebound hypoglycemia regardless of individual difference among East Asian in insulin responses.

Insulin has a potential to inhibit lipolysis which leads to a reduction in availability of FFA (14). Actually, induction of hyperinsulinemia state by pre-exercise ingestion of a high glycemic index (HGI) CHO, such as glucose or other HGI meal, at the onset of exercise decreased plasma FFA levels and increased respiratory exchange ratio (RER) or suppressed fat oxidation during exercise compared with the non-hyperinsulinemia state in Western population (3–5, 9, 10, 15, 21, 35–37). Furthermore, a reduction in availability of FFA during exercise increases muscle glycogen utilization to compensate energy demand (38). Sparks et al. (39) have suggested that increased CHO oxidation early during exercise after a HGI meal reflect an increase in glycogen utilization. In the present study, although fat oxidation rates during exercise in the LOW group were similar between the G and P trial, in the HIGH group fat oxidation rates during exercise in the G trial was significantly lower than that in the P trial. However, interestingly, CHO oxidation rates during exercise in the HIGH group were similar in the two trials. As previously mentioned, it is assumed that insulin secretory capacity of our subjects is genetically low (25, 34); similarly, we observed that rebound hypoglycemia did not occur in both the groups, thus supporting this assumption. Therefore, although fat oxidation in the HIGH group was decreased by insulin, this effect of inhibition is not significant and muscle glycogen utilization was not augmented. This also explains why endurance capacity was not decreased in this study because it was hypothesized that reduced endurance capacity by pre-exercise CHO ingestion is attributed to augmentation of glycogenolysis (5, 6). These results suggest that pre-exercise glucose ingestion in East Asian athletes do not accelerate muscle glycogen breakdown, although fat utilization may be suppressed, depending on individual difference in insulin responses.

In this study, time to exhaustion in the G trial was approximately 33.8% longer than in the P trial in the LOW group, although there was no significant difference between the two trials in the both group. Endurance capacity has been associated with a capacity to maintain blood glucose levels late during exercise because blood glucose is used to produce energy as a compensation for decreased muscle glycogen (1, 2). DeMarco et al. (35) reported that low GI (LGI) meal feeding 30 min before exercise significantly increased blood glucose levels late during exercise compared with HGI meal and water and, thus, improved an exhaustion time compared with HGI meal and water. In the LOW group, blood glucose levels during exercise in the G trial was significantly higher than that in the P trial, which indicates that blood glucose was maintained at a higher level due to glucose feeding compared with non-feeding state. Because substrate oxidation in the LOW group was not affected by glucose induced insulin response, ingested glucose was used to produce energy late during exercise as an additional energy substrate and thus performance might increase. Meanwhile, time to exhaustion did not change in the HIGH group may be due to reduced fat oxidation. Thus, it is speculated that ingested glucose was used to produce energy as a compensation for reduction in fat-derived energy substrate, resulting in no improvement in performance. These results suggest a possibility that pre-exercise glucose ingestion in East Asians with low insulin response improves endurance performance.

Muscle fatigue can also occur as a result of a disruption of any link from the central nervous system (CNS) to the contractile muscle tissue (40). Glucose is a main energy source for the CNS; therefore, hypoglycemia during exercise attenuate CNS activation (41). Nybo (41) have reported that CHO supplementation during exercise prevented hypoglycemia and maintained CNS activation. CFF is a visual identification task designed to evaluate overall CNS activity (42), and it changes according to the activation of CNS or change in arousal level owing increased fatigue; thus, this is reflected as a decreased CFF with accumulation of CNS fatigue (43). In this study, amount of variations of CFF in the LOW and HIGH group showed a plus value, which indicated that CNS activation did not decrease, but improved instead. Presland et al. (44) reported that CFF
significantly increases after cycling at 70% peak VO2 until exhaustion, similar to the findings of our study. We assumed that in our protocol, CNS was activated and CFF increased. However, the CFF values in the LOW group shows a tendency to increase in the G trial compared with the P trial. Because blood glucose levels in the LOW group was maintained at a higher level by glucose feeding compared with non-feeding state, we speculate that glucose supply for CNS is maintained and provide the positive effect on CNS. These results suggest that CNS fatigue was not a cause of stopping the exercise and that pre-exercise glucose ingestion have a positive effect on CNS function in East Asian with low insulin response.

In this study, amount of variations of RPE during exercise in the HIGH group showed higher tendency in the G trial compared with the P trial. Accordingly, the fatigue categories of Group III of “Study of fatigue feelings” in the HIGH group was significantly higher than that in the P trial. Because it is considered that muscle glycogen utilization is not augmented and rebound hypoglycemia is not occur, we could not explain the reason why subjective fatigue in HIGH group increased by glucose feeding. That increase in subjective fatigue by glucose feeding may prevent an improvement in endurance performance. Further studies are needed to clarify the cause of this phenomenon.

In conclusion, these data suggest that pre-exercise ingestion of 1.5 g/kg body mass in East Asian student athletes does not induce rebound hypoglycemia and does not reduce their endurance capacity regardless of differences in individual insulin responses. Furthermore, individuals with low insulin responses seem to improve endurance performance with glucose ingestion before exercise. Further studies need to analyze insulin concentration and FFA in a larger cohort.

Disclosure of state of COI
No conflicts of interest to be declared.

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