Effects of preoperative and intraoperative glucose administration on glucose use and fat catabolism during laparotomy under sevoflurane anesthesia in fasted rats

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Abstract Preoperative fasting as well as surgical stress significantly modifies metabolisms. Recent studies reported the possible advantageous effects of glucose administration on perioperative metabolisms; however, the underlying mechanisms have not been fully elucidated. Rats were allocated to three groups. During the fasting period, groups A and B were administered water, but group C was administered glucose. During laparotomy and the insulin tolerance test (ITT) under sevoflurane anesthesia, group A was administered saline, but groups B and C were administered glucose. During laparotomy, group C showed higher glucose levels and lower β-hydroxybutyrate (β-OHB) levels than group A, and group B showed more decreases in β-OHB levels than group A without differences in changes in glucose levels. Insulin levels and insulin sensitivity during laparotomy were similar among the three groups. No significant difference in insulin sensitivity was also confirmed in ITT. In conclusion, perioperative glucose administration suppresses lipolysis without affecting insulin secretion and sensitivity.

Keywords Intraoperative glycemic control · Insulin secretion · Insulin sensitivity · β-Hydroxybutyrate · Adipocytokine

Introduction

Assurance of an energy demand/supply balance is important in perioperative management. In clinical settings, most patients are made to fast prior to surgery. Fasting causes an energy demand/supply imbalance, leading to considerable changes in metabolism [1]. Carbohydrates, protein and fat are reserved as substrates for the energy supply in the body: the reserved amount of carbohydrates is much less than that of protein and fat [2]. Carbohydrates are mainly stored as liver glycogen, which is rapidly consumed during a short-term starvation; the lack of a sufficient energy supply via glycolysis induces proteolysis and lipolysis for gluconeogenesis [2, 3]. Surgical stress modifies glucose metabolism. The endocrine-metabolic responses to surgical stress increase the secretion of catabolic hormones such as catecholamine, cortisol and glucagon, by which glycolysis, proteolysis and lipolysis are accelerated, leading to the enhancement of glucose production [1]. Furthermore, surgical stress exaggerates insulin resistance, resulting in the impairment of glucose use [1]. It was reported that carbohydrate loading during the fasting period (i.e., intake of a carbohydrate-rich drink) ameliorates postoperative insulin resistance [4–6]. A recent animal study [7] and recent clinical study [8] suggested that intraoperative glucose administration suppresses proteolysis and lipolysis during surgery. However, the precise mechanisms underlying the effects of pre- and intraoperative glucose administration on metabolism during surgery have not been elucidated. General anesthetics are categorized into volatile and intravenous anesthetics. Generally, a kind of volatile anesthetic in combination with intravenous anesthetics is administered during surgery under general anesthesia. In Japan, sevoflurane, a kind of volatile anesthetic, is one of the most common agents for maintenance of general anesthesia.
anesthesia in clinical settings. Here, we examined the effects of pre- and intraoperative glucose administration on plasma insulin levels, insulin sensitivity and fat catabolism during laparotomy under sevoflurane anesthesia in fasted rats.

**Methods**

This study was approved by the animal care committee of The University of Tokyo (protocol no. H13-047). The experimental protocols are summarized in Fig. 1.

**Subjects**

We used 9–11-week-old male Wistar rats (Nippon Bio-Supply Center, Tokyo, Japan). Rats were housed in a regulated environment and allowed free access to a standard diet (Oriental Yeast Co., Ltd., Tokyo, Japan) and water: ambient temperature of 25 °C with a 12-h light-dark cycle (7 a.m. and 7 p.m.). Rats were assigned to three groups: groups A, B and C (7 rats per group). All rats were fasted for 12 h prior to the experiments. During the fasting period, rats in groups A and B were provided with water, whereas rats in group C were provided with 12.5 % glucose. We conducted the experiments between 8 a.m. and 12 a.m.

**Preparations**

Just before induction of general anesthesia, we punctured the tail vein and measured blood glucose and β-hydroxybutyrate (β-OHB) levels (T1), following which each rat was anesthetized and underwent surgical preparation: tracheotomy, tracheal intubation and insertion of catheters into the right carotid artery and right jugular vein. Anesthesia was provided with sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). For induction of anesthesia, sevoflurane (5 % in 1 l/min oxygen) was administered via a face mask. After tracheal intubation, sevoflurane (2.5 % in 1 l/min oxygen) was administered via a tracheal tube for maintenance of anesthesia, and the lungs were mechanically ventilated.

All rats were administered 100 IU of heparin intravenously to maintain patency of the catheters. The arterial catheter was connected to a low-volume pressure transducer for monitoring mean arterial blood pressure (MAP) and heart rate (HR). Surgical preparation took approximately 30 min in each rat.

After surgical preparation, rats in group A were administered physiological saline (10 ml/kg/h) intravenously, whereas rats in groups B and C were administered physiological saline (9.5 ml/kg/h) with 50 % glucose (0.5 ml/kg/h) intravenously. A 30-min stabilization period was allowed. Then, 1 ml of arterial blood was sampled (T2), following which rats underwent laparotomy.

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**Fig. 1** The experimental protocol. All rats were fasted for 12 h prior to the experiment. During the fasting period, rats in groups A and B were provided with water, whereas rats in group C were provided with 12.5 % glucose. General anesthesia was induced and maintained using sevoflurane in all rats. After surgical preparation, rats in group A were administered saline intravenously, whereas rats in groups B and C were administered saline with glucose intravenously. A 30-min stabilization period was allowed. Then, all rats underwent laparotomy and the insulin tolerance test. T1 just before induction of anesthesia. T2 just before laparotomy. T3 just after laparotomy (i.e., just before insulin administration). T4 at 15 min after insulin administration.
Laparotomy

We performed a midline laparotomy (the incision was 5 cm in length), applied a wound retractor to the abdominal wall for 5 min and closed the abdomen; these procedures took just 15 min in each rat.

The insulin tolerance test (ITT)

At the end of laparotomy, 1 ml of arterial blood was sampled (T3). Immediately after laparotomy, all rats were subjected to the ITT; 10 IU/kg of rapid-acting human insulin analog (Humalin R; Eli Lilly Japan K.K., Hyogo, Japan) was administered intravenously [9–11]. Fifteen minutes after the insulin administration, 0.2 ml of arterial blood was sampled (T4).

Measurements

Immediately after each blood sampling, arterial PO2, arterial PCO2, base excess, glucose levels and blood β-OHB levels were examined. We used the i-STAT 1 Analyzer (Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) and Precision Xceed (Abbott Japan Co., Ltd., Tokyo, Japan) for arterial blood gas analyses. Blood glucose and β-OHB levels were measured using Medisafe (Terumo, Tokyo, Japan) and high-molecular-weight adiponectin (HMW-adiponectin) levels were measured by the enzyme-linked immunosorbent assay using AKRIN-010T, AKRTN-010 and AKMAN-011 (Shibayagi Co., Ltd., Gunma, Japan), respectively.

Calculations

Changes in blood glucose levels during preparations were calculated using the following equation: Δglucose [preparations] (mg/dl) = [blood glucose levels at T2 (mg/dl)] − [blood glucose levels at T1 (mg/dl)]. Changes in blood glucose levels during laparotomy were calculated using the following equation: Δglucose [laparotomy] (mg/dl) = [blood glucose levels at T3 (mg/dl)] − [blood glucose levels at T2 (mg/dl)].

Changes in blood β-OHB levels during preparations were calculated using the following equation: Δβ-OHB [preparations] (mmol/l) = [blood β-OHB levels at T2 (mmol/l)] − [blood β-OHB levels at T1 (mmol/l)]. Changes in blood β-OHB levels during laparotomy were calculated using the following equation: Δβ-OHB [laparotomy] (mmol/l) = [blood β-OHB levels at T3 (mmol/l)] − [blood β-OHB levels at T2 (mmol/l)].

We calculated the quantitative insulin sensitivity check index (QUICKI) at each time point using the following equation: QUICKI = 1/ (log [plasma insulin level at each time point (μU/ml)] + log [blood glucose level at each time point (mg/dl)]) [12].

Statistical analyses

Parametric data are shown as mean ± SD. Mauchly’s test was used to check the sphericity condition; statistical significance was set as P < 0.05. For overall comparisons of serial data among the three groups, two-way repeated measures analysis of variance (ANOVA), with group and time point as the factors, was used. When the sphericity condition was met, statistical significance was set at P < 0.05 for two-way repeated-measures ANOVA. When the sphericity condition was not met, Greenhouse-Geisser correction was applied, and statistical significance was set at adjusted P < 0.05 for two-way repeated-measures ANOVA. Homogeneity of variance was examined using the Bartlett test; statistical significance was set at P < 0.05. We used one-way ANOVA for comparisons of parametric data at each time point among the three groups, we used the Kruskal-Wallis test; statistical significance was set at P < 0.05.

Statistical analyses were performed using JMP version 10.0.2. (SAS Institute, Cary, NC).

Results

Rats in groups A, B and C weighed 309 ± 26, 301 ± 25 and 300 ± 32 g, respectively; there was no significant difference among the three groups (P = 0.7836, 1-way ANOVA).

Table 1 shows MAP, HR, arterial PO2, arterial PCO2 and base excess during laparotomy. There were no significant differences in MAP at T2 and T3 among the three groups (P = 0.4975 and 0.6457, respectively, 1-way ANOVA). There were no significant differences in HR at T2 and T3 among the three groups (P = 0.2631 and
Parametric data are shown as mean ± SD. *Adjusted P < 0.05 versus group A at each time point, Tukey-Kramer HSD test.

There were no significant differences in arterial PO₂ at T2 and T3 among the three groups (P = 0.9890 and 0.7993, respectively, 1-way ANOVA). There was a significant difference in arterial PCO₂ at T2 among the three groups (P = 0.028, 1-way ANOVA); group C showed significantly higher arterial PCO₂ than group A (adjusted P = 0.0300 Tukey-Kramer HSD test). There was no significant difference in arterial PCO₂ at T3 among the three groups (P = 0.9330, 1-way ANOVA). There were no significant differences in base excess at T2 and T3 among the three groups (P = 0.3079 and 0.1407, respectively, 1-way ANOVA).

Time courses of blood glucose levels from T1 to T4 are shown in Table 2. There was no significant difference in the time courses of blood glucose levels among the three groups (adjusted P = 0.4010, 2-way repeated-measures ANOVA with Greenhouse-Geisser correction). There were significant differences in blood glucose levels among the three groups at T1, T2, T3 and T4 (P = 0.0253, 0.0003, 0.0002 and 0.0005, respectively, 1-way ANOVA). Group B showed significantly higher blood glucose levels than group A at T2 (adjusted P = 0.0456, Tukey-Kramer HSD test). Group C showed significantly higher blood glucose levels than group A at T1, T2, T3 and T4 (adjusted P = 0.0320, 0.0002, 0.0001 and 0.0004, respectively, Tukey-Kramer HSD test); in addition, group C showed significantly higher blood glucose levels than group B at T3 and T4 (adjusted P = 0.0143 and 0.0306, respectively, Tukey-Kramer HSD test). Changes in blood glucose levels during preparations, laparotomy and ITT are shown in Fig. 2. There was no significant difference in Δglucose (preparations) among the three groups (P = 0.3636, 1-way ANOVA). There was no significant difference in Δglucose (laparotomy) among the three groups (P = 0.3854, 1-way ANOVA). There was also no significant difference in Δglucose (ITT) among the three groups (P = 0.9959, 1-way ANOVA).

Plasma insulin, TNF-α and HMW-adiponectin levels and QUICKI during laparotomy are shown in Table 3. There were no significant differences in plasma insulin levels among the three groups at T2 and T3 (P = 0.4832 and 0.3699, respectively, Kruskal-Wallis test). TNF-α was not detected in all rats at T2. TNF-α was not detected in all rats in groups A and B at T3, but detected in one out of seven rats in group C; there was no significant difference among the three groups (P = 0.3679, Kruskal-Wallis test). There were no significant differences in plasma HMW-adiponectin levels among the three groups at T2 and T3 (P = 0.6293 and 0.8310, respectively, Kruskal-Wallis test). There were no significant differences in QUICKI among the three groups at T2 and T3 (P = 0.2801 and 0.1587, respectively, Kruskal-Wallis test).

Time courses of blood β-OHB levels from T1 to T3 are shown in Table 4. There was a significant difference in the time courses of blood β-OHB levels among the three groups (P = 0.0014, 2-way repeated-measures ANOVA). There were significant differences in blood β-OHB levels among the three groups at T1, T2 and T3 (P < 0.0001, = 0.0009 and <0.0001, respectively, 1-way ANOVA).

### Table 1: Mean arterial blood pressure, heart rate, arterial PO₂, arterial PCO₂ and base excess during laparotomy

|                | T2      | T3      |
|----------------|---------|---------|
| **Mean arterial blood pressure (mmHg)** |          |         |
| Group A        | 77 ± 22 | 84 ± 14 |
| Group B        | 86 ± 28 | 90 ± 18 |
| Group C        | 92 ± 18 | 92 ± 15 |
| **Heart rate (beats/min)**               |          |         |
| Group A        | 379 ± 46| 359 ± 44|
| Group B        | 375 ± 40| 382 ± 50|
| Group C        | 407 ± 21| 373 ± 27|
| **Arterial PO₂ (mmHg)**                  |          |         |
| Group A        | 459 ± 75| 470 ± 100|
| Group B        | 466 ± 78| 491 ± 71 |
| Group C        | 462 ± 82| 464 ± 59 |
| **Arterial PCO₂ (mmHg)**                 |          |         |
| Group A        | 33.6 ± 1.7| 34.6 ± 2.8 |
| Group B        | 34.4 ± 2.8| 33.9 ± 2.0 |
| Group C        | 37.4 ± 2.8*| 33.9 ± 5.1 |
| **Base excess (mmol/l)**                 |          |         |
| Group A        | 0.7 ± 1.3| 0.4 ± 1.5 |
| Group B        | 2.4 ± 3.2| 1.6 ± 3.0 |
| Group C        | 2.3 ± 1.9| −1.0 ± 2.1 |

Parametric data are shown as mean ± SD. T2 just before laparotomy, T3 just after laparotomy. *Adjusted P < 0.05 versus group A at each time point, Tukey-Kramer HSD test.

### Table 2: Blood glucose levels during laparotomy and the insulin tolerance test

|                | T1      | T2      | T3      | T4      |
|----------------|---------|---------|---------|---------|
| **Blood glucose levels (mg/dl)** |          |         |         |         |
| Group A        | 60 ± 17 | 94 ± 15 | 102 ± 14| 26 ± 5  |
| Group B        | 63 ± 16 | 113 ± 13*| 121 ± 10| 45 ± 15 |
| Group C        | 86 ± 20*| 132 ± 13*| 146 ± 20*| 71 ± 26*|

Parametric data are shown as mean ± SD. T1 just before induction of general anesthesia. T2 just before laparotomy. T3 just after laparotomy (i.e., just before insulin administration). T4 at 15 min after insulin administration. *Adjusted P < 0.05 versus group A at each time point, Tukey-Kramer HSD test.
ANOVA). Group B showed significantly lower blood β-OHB levels than group A at T3 (adjusted \( P = 0.0059 \), Tukey-Kramer HSD test). Group C showed significantly lower blood β-OHB levels than group A at T1, T2 and T3 (adjusted \( P < 0.0001 \), \( 0.0007 \) and \(<0.0001\), respectively, Tukey-Kramer HSD test); in addition, group C showed significantly lower blood β-OHB levels than group B at T1 and T2 (adjusted \( P = 0.0003 \) and 0.0190, respectively, Tukey-Kramer HSD test). Changes in blood β-OHB levels during preparation and laparotomy are shown in Fig. 3. There was no significant difference in Δβ-OHB (preparations) among the three groups (\( P = 0.2600\), 1-way ANOVA). There was a significant difference in Δβ-OHB (laparotomy) among the three groups (\( P = 0.016\), 1-way ANOVA). Group B showed significantly more decrease in blood β-OHB levels during laparotomy than group A (adjusted \( P = 0.0214 \), Tukey-Kramer HSD test), while group C showed a similar decrease in blood β-OHB levels during laparotomy in comparison with group A (adjusted \( P = 0.9177 \), Tukey-Kramer HSD test). In addition group B showed significantly more decrease in β-OHB during laparotomy than group C (adjusted \( P = 0.0481 \), Tukey-Kramer HSD test).

**Table 3** Plasma insulin, tumor necrosis factor-α and high-molecular-weight adiponectin levels and the quantitative insulin sensitivity check index during laparotomy

|                  | T2                  | T3                  |
|------------------|---------------------|---------------------|
| **Plasma insulin levels (μIU/ml)** |                     |                     |
| Group A          | 23 (18, 125)        | 19 (13, 66)         |
| Group B          | 39 (18, 143)        | 31 (21, 56)         |
| Group C          | 51 (29, 107)        | 50 (29, 79)         |
| **Plasma tumor necrosis factor-α levels (pg/ml)** |                     |                     |
| Group A          | 0 (0, 0)            | 0 (0, 0)            |
| Group B          | 0 (0, 0)            | 0 (0, 0)            |
| Group C          | 0 (0, 0)            | 0 (0, 0)            |
| **Plasma high-molecular-weight adiponectin levels (ng/ml)** |                     |                     |
| Group A          | 718 (625, 832)      | 767 (271, 826)      |
| Group B          | 959 (508, 991)      | 739 (492, 1024)     |
| Group C          | 684 (419, 1400)     | 606 (536, 996)      |
| **Quantitative insulin sensitivity check index** |                     |                     |
| Group A          | 0.299 (0.243, 0.308)| 0.301 (0.266, 0.318)|
| Group B          | 0.277 (0.238, 0.301)| 0.284 (0.260, 0.291)|
| Group C          | 0.262 (0.238, 0.278)| 0.253 (0.244, 0.277)|

Nonparametric data are shown as median (25th, 75th percentiles)

**T2** just before laparotomy. **T3** just after laparotomy

**Table 4** Blood β-hydroxybutyrate levels during laparotomy

|                  | T1                  | T2                  | T3                  |
|------------------|---------------------|---------------------|---------------------|
| **Blood β-hydroxybutyrate levels (mmol/l)** |                     |                     |                     |
| Group A          | 1.3 ± 0.2           | 1.0 ± 0.3           | 0.9 ± 0.3           |
| Group B          | 1.3 ± 0.3           | 0.7 ± 0.3           | 0.5 ± 0.3*          |
| Group C          | 0.7 ± 0.2*          | 0.3 ± 0.2*          | 0.2 ± 0.1*          |

Parametric data are shown as mean ± SD

**T1** just before induction of general anesthesia. **T2** just before laparotomy. **T3** just after laparotomy

* Adjusted \( P < 0.05 \) versus group A at each time point, Tukey-Kramer HSD test.

Fig. 2 Changes in blood glucose levels during the experiments.

a Shows the increases in blood glucose levels during preparations [Δglucose (preparations)]; there was no significant difference among the three groups (\( P > 0.05, 1\)-way ANOVA).

b Shows the increases in blood glucose levels during laparotomy [Δglucose (laparotomy)]; there was no significant difference among the three groups (\( P > 0.05, 1\)-way ANOVA).

c Shows the decreases in blood glucose levels during the insulin tolerance test [Δglucose (ITT)]; there was no significant difference among the three groups (\( P > 0.05, 1\)-way ANOVA).
Discussion

Group C showed higher blood glucose levels and lower blood \( \beta \)-OHB levels during surgery compared to groups A and B (adjusted \( P = 0.0214 \), Tukey-Kramer HSD test) and between groups A and C (adjusted \( P = 0.0048 \), Tukey-Kramer HSD test), while no significant difference was detected between groups A and C (adjusted \( P > 0.05 \), Tukey-Kramer HSD test).

Glucose use is regulated by plasma insulin levels as well as insulin sensitivity. Volatile anesthetics, such as sevoflurane, activate adenosine triphosphate-sensitive potassium channels in \( \beta \)-islet cells and attenuate insulin secretion from \( \beta \)-islet cells [13–16]. There were no significant differences in plasma insulin levels during laparotomy among groups A, B and C, although significant differences in blood glucose levels were observed. We speculate that these results reflect the inhibitory effect of sevoflurane on glucose-induced insulin secretion.

Insulin sensitivity is another factor regulating glucose use. There were no significant differences in \( \Delta \)glucose [ITT] among groups A, B and C. There was no significant difference in QUICKI during laparotomy among groups A, B and C. Several studies reported the involvement of adipocytokines, such as TNF-\( \alpha \) and HMW-adiponectin, in insulin sensitivity; increased TNF-\( \alpha \) levels were associated with insulin resistance, and decreased HMW-adiponectin levels were associated with insulin resistance [17–21]. There were no significant differences in plasma TNF-\( \alpha \) and HMW-adiponectin levels during laparotomy among groups A, B and C. These results suggest that preoperative and intraoperative glucose administration does not affect insulin sensitivity during surgery under sevoflurane anesthesia.

Taken together, results in this study suggest four major impacts of pre- and intraoperative glucose administration on glucose metabolism and fat catabolism in fasted rats undergoing surgery under sevoflurane anesthesia. First, preoperative glucose administration can ameliorate the energy demand/supply imbalance enhanced by fasting. Second, pre- and intraoperative glucose administration produces no significant effects on plasma insulin levels during surgery under sevoflurane anesthesia. Third, pre- and intraoperative glucose administration does not affect insulin sensitivity during surgery under sevoflurane anesthesia. Fourth, glucose administration alone can effectively suppress fat catabolism during surgery under sevoflurane anesthesia. Although we cannot simply extrapolate the findings in this animal study to clinical practice, pre- and intraoperative glucose administration may provide patients undergoing surgery with advantageous effects on metabolism.

During the preoperative fasting period, rats in group C were allowed free access to a bottle filled with 12.5 % glucose. Therefore, it was difficult to measure the accurate amount of glucose taken by each rat during the fasting period. After surgical preparation, rats in group B were administered glucose intravenously at a rate of 250 mg/kg/h, and this dose of glucose significantly suppressed intraoperative lipid catabolism. We consider that further investigations are required to elucidate the minimal dose of glucose for the suppression of lipid catabolism during surgery under sevoflurane anesthesia.
We believe that the surgical stress applied to rats in this study was not small. The incision was 5 cm long, and we applied the wound retractor for 5 min to generate visceral pain. However, we could not detect TNF-α in plasma in almost all rats in this study. Therefore, the surgical stress may be smaller than that of major surgery in clinical settings, such as hepatectomy, total gastrectomy and cardiac surgery. We suppose that the results in this study should be verified by further investigations in which strong surgical stress compatible to major surgery in clinical settings is applied to test animals.

In this study, we used normal rats, but not diabetic rats. Results in this study suggest that perioperative glucose administration has no significant effects on insulin sensitivity during surgery under sevoflurane anesthesia. We thus consider that the results in this study should also be verified by further investigations using diabetic rats. Sevoflurane anesthesia might be an efficient regimen of anesthetic management for diabetic patients undergoing surgery.

The major limitation of this study is the method applied for the evaluation of insulin sensitivity. The standard method to evaluate insulin sensitivity is the hyperinsulinemic normoglycemic clamp [22]; however, we evaluated insulin sensitivity by QUICKI and ITT. Due to the study design, it was impractical to apply the hyperinsulinemic normoglycemic clamp for evaluation of insulin sensitivity in this study. QUICKI is considered a useful and practical index to evaluate insulin sensitivity. The standard method to evaluate insulin sensitivity is the hyperinsulinemic normoglycemic clamp [22]; however, we evaluated insulin sensitivity by QUICKI and ITT. Due to the study design, it was impractical to apply the hyperinsulinemic normoglycemic clamp for evaluation of insulin sensitivity in this study. QUICKI is considered a useful and practical index to evaluate insulin sensitivity in clinical settings: fasting blood samples are required to measure QUICKI [12, 23, 24]. Although some studies reported the usefulness of QUICKI in animal studies to evaluate insulin sensitivity [25, 26], further investigations applying the hyperinsulinemic normoglycemic clamp may be required to confirm the effects of pre- and intraoperative glucose administration on insulin sensitivity during surgery under sevoflurane anesthesia.

In conclusion, pre- and intraoperative glucose administration effectively suppresses fat catabolism without affecting plasma insulin levels as well as insulin sensitivity during laparotomy under sevoflurane anesthesia in fasted rats.

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Compliance with ethical standards

Conflict of interest There is no conflict to disclose.

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