Original Article

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Comparison of mechanisms underlying changes in glucose utilization in fasted rats anesthetized with propofol or sevoflurane: Hyperinsulinemia is exaggerated by propofol with concomitant insulin resistance induced by an acute lipid load

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Summary **The effects of anesthesia with sevoflurane and with propofol on glucose utilization in rats were investigated. Sevoflurane significantly impairs glucose utilization whereas propofol does not. Both insulin secretion and sensitivity affect glucose utilization. Propofol is hydrophobic, and anesthesia with this agent is always accompanied by an acute lipid load, which can exaggerate insulin resistance. The role of the acute lipid load in the effects of anesthesia with sevoflurane and propofol on glucose utilization in fasted rats was investigated. Rats were allocated to groups anesthetized with sevoflurane and infused with physiological saline (group S) or 10% w/v lipid (group SL), or those anesthetized with propofol (group P). Intravenous glucose tolerance tests and insulin tolerance tests were then performed to measure glucose utilization, and blood glucose, plasma insulin, and plasma TNF-α levels were measured. In the intravenous glucose tolerance test, groups SL and P showed significantly higher plasma insulin levels than group S, and group P showed significantly higher plasma insulin levels than group SL. In the insulin tolerance test, groups SL and P showed insulin resistance compared to group S, but no significant difference was observed between groups SL and P. In summary, propofol anesthesia enhances insulin secretion and concomitantly exaggerates insulin resistance, compared with sevoflurane anesthesia. Propofol appears to be the main cause of hyperinsulinemia, and the acute lipid load exaggerates insulin resistance.**

Keywords: General anesthesia, insulin secretion, insulin sensitivity, lipid metabolism, tumor necrosis factor-α

1. Introduction

We previously investigated the effects of anesthesia with different agents on glucose metabolism in rats and found that sevoflurane impairs glucose utilization, while propofol does not (*1*). Volatile anesthetics, such as sevoflurane, activate adenosine triphosphate-sensitive potassium channels in β-islet cells, resulting in attenuated insulin secretion (*2-5*). Although the precise mechanisms have not been elucidated, insulin secretion is significantly enhanced in rats under propofol anesthesia (*6,7*). Plasma insulin levels and insulin sensitivity regulate glucose utilization. Our recent findings suggested that insulin sensitivity is significantly impaired by propofol anesthesia compared with sevoflurane anesthesia (*7*). Due to the hydrophobic properties of propofol, a lipid formulation is generally used for anesthesia, and this imposes an acute lipid load. Recent studies (*8-11*) have shown that an acute lipid load exaggerates insulin resistance. Therefore, the role of an acute lipid load in the effects of anesthesia with sevoflurane and propofol on insulin secretion and sensitivity were investigated in fasted rats.

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2. Materials and Methods

2.1. *Subjects*

The Animal Care Committee of The University of Tokyo approved the experimental protocols (Approval number: H13-047) in this study (Figures 1 and 2). Nine- to 10-week-old, male Wistar rats were housed in a regulated environment at an ambient temperature of 25°C under a 12-hour light-dark cycle (7 AM and 7 PM). Water and a standard diet comprised of 24% protein, 5% fat, 6% ash, 3% fiber, 8% water, and 54% nitrogen-free extract were provided *ad libitum*, and all rats were fasted for 12 h before starting the study. Hypothermia was prevented during the experiments using a heat lamp and a heating pad.

2.2. *Surgical preparation*

Anesthesia was induced with 5% sevoflurane (Maruishi Pharmaceutical Co. Ltd., Osaka, Japan) in 1.5 L/min oxygen administered *via* a tightly fitting face mask in 42 rats during surgical preparation. All rats underwent tracheotomy and tracheal intubation. Sevoflurane (2.5% in 0.5 L/min oxygen) was administered *via* the tracheal tube, and the lungs were mechanically ventilated at a tidal volume of 2.5 mL and a respiratory rate of 55 breaths/min. A 19-gauge catheter was inserted into the right carotid artery, and another catheter was inserted into the right jugular vein. Catheter patency was maintained with 100 IU of intravenous heparin. Hemodynamic variables were recorded, and 1.5 mL of arterial blood was sampled immediately after surgical preparation (T1).

2.3. *Intravenous glucose tolerance test (IVGTT)*

The administered doses of sevoflurane and propofol for maintenance of anesthesia were selected based on our previous protocols (*1,6,7*). Twenty-one rats were assigned to groups S-IVGTT, SL-IVGTT, and P-IVGTT (n = 7 in each group; Figure 1). Sevoflurane anesthesia was continued in groups S-IVGTT and SL-IVGTT. In group S-IVGTT, physiological saline was administered intravenously with a 4 mL/kg bolus, followed by continuous infusion at a rate of 4 mL/kg/h. In group SL-IVGTT, 10% w/v Intralipid (Fresenius Kabi Japan K.K., Tokyo, Japan) was administered intravenously with a 4 mL/kg bolus, followed by continuous infusion at a rate of 4 mL/kg/h. In group P-IVGTT, sevoflurane administration was discontinued, and instead, 10 mg/mL of propofol solution (1% Diprivan; AstraZeneca K.K., Osaka, Japan) was administered intravenously with a 4 mL/kg bolus, followed by continuous infusion at a rate of 4 mL/kg/h. After stabilization for 30 min, 1 g/kg of glucose was administered intravenously to all rats for the IVGTT. Hemodynamic variables were recorded, and 1.5 mL of arterial blood was sampled, immediately before (T2) and at 15 (T3) and 30 (T4) min after glucose administration. The lipid loads were equal in groups SL-IVGTT and P-IVGTT.

2.4. *Insulin tolerance test (ITT)*

The administered doses of sevoflurane and propofol were selected as described above. Another 21 rats were assigned to groups S-ITT, SL-ITT, and P-ITT (n = 7 in each group; Figure 2), surgically prepared as described above, and given 10% glucose at a rate of 10 mL/kg/h intravenously. Sevoflurane anesthesia was continued in groups S-ITT and SL-ITT, which then received intravenously a 4 mL/kg bolus of physiological saline or 10% w/v intralipid, followed by a continuous infusion at a rate of 4 mL/kg/h of physiological saline or 10% w/v intralipid, respectively. In group P-ITT, sevoflurane administration was discontinued, and instead, 1% diprivan was administered intravenously with a 4 mL/kg bolus, followed by continuous infusion at a rate of 4 mL/kg/h. After stabilization for 30 min, 10 IU/kg of the rapid-acting human insulin analogue (Humulin-R; Eli Lilly Japan K.K., Hyogo, Japan) was administered intravenously to all groups for the ITT (*12-14*). Hemodynamic variables were recorded, and 1.5 mL of arterial blood was sampled immediately before (T2) and at 15 (T3) and 30 (T4) min after insulin administration. The lipid loads were equal in groups SL-ITT and P-ITT.

2.5. *Measurements*

The arterial catheter was connected to a low-volume pressure transducer to monitor mean arterial blood pressure (MAP) and heart rate (HR). Immediately after each blood sampling, blood glucose and β-hydroxybutyrate (β-OHB) levels were measured using Medisafe (Terumo, Tokyo, Japan) and Precision Xceed (Abbott Japan Co. Ltd., Tokyo, Japan), respectively. Blood samples were spun in a prerefrigerated centrifuge (4°C) at 1000× g for 15 min, and plasma specimens were stored at -60°C. Plasma insulin and TNF-α levels were measured using AKRIN-010T and AKRTN-010 enzyme-linked immunosorbent assays, respectively (Shibayagi Co. Ltd., Gunma, Japan).

The quantitative insulin sensitivity check index (QUICKI) was calculated using the following equation: QUICKI = 1/(log [plasma insulin level (μIU/mL)] + log [blood glucose level (mg/dL)]) (*15*). The area under the time-response curve above the glucose level at T2 in each rat was calculated to evaluate changes in blood glucose levels during the IVGTT (AUC [T2-T4]). In addition, Δglucose [T2-T4] was calculated to evaluate changes in blood glucose levels during the ITT using the following equation: Δglucose [T2-T4] (mg/dL) = [blood glucose level at T4 (mg/dL)] - [blood glucose level at T2 (mg/dL)].

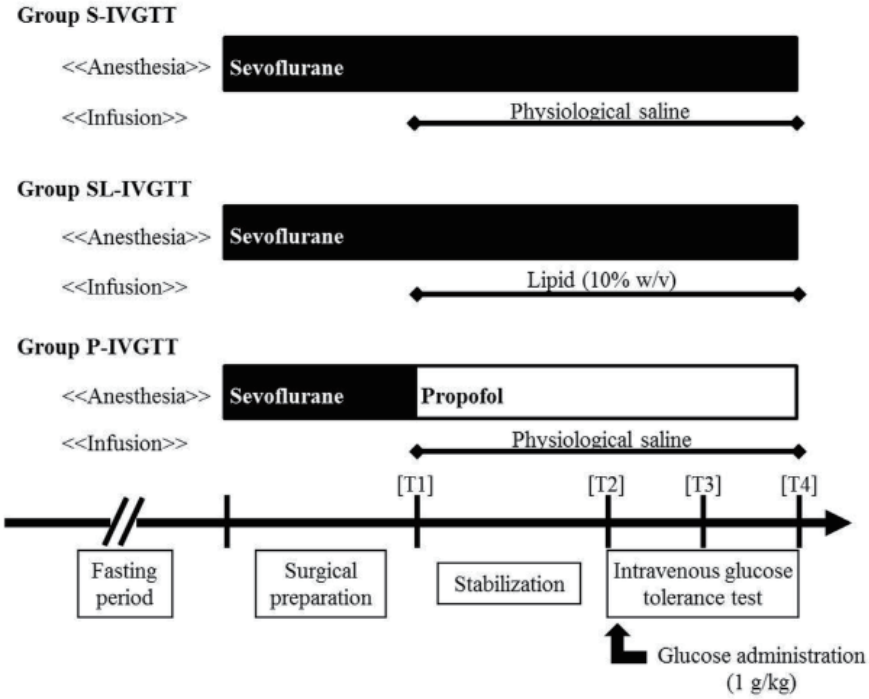

Figure 1. Experimental protocols for intravenous glucose tolerance tests (IVGTT). A set of 21 rats underwent surgical preparation under sevoflurane anesthesia. Rats were assigned to 3 groups: groups S-IVGTT, SL-IVGTT, and P-IVGTT. Sevoflurane anesthesia was continued in groups S-IVGTT and SL-IVGTT. Physiological saline was administered intravenously in group S-IVGTT, while 10% w/v lipid was administered intravenously in group SL-IVGTT. Sevoflurane administration was discontinued, and instead propofol solution was administered intravenously in group P-IVGTT. After a 30-min stabilization period, the intravenous glucose tolerance test was performed. Hemodynamic variables were recorded, and arterial blood was sampled immediately after surgical preparation (T1), immediately before (T2), and at 15 min (T3) and 30 min (T4) after glucose administration.

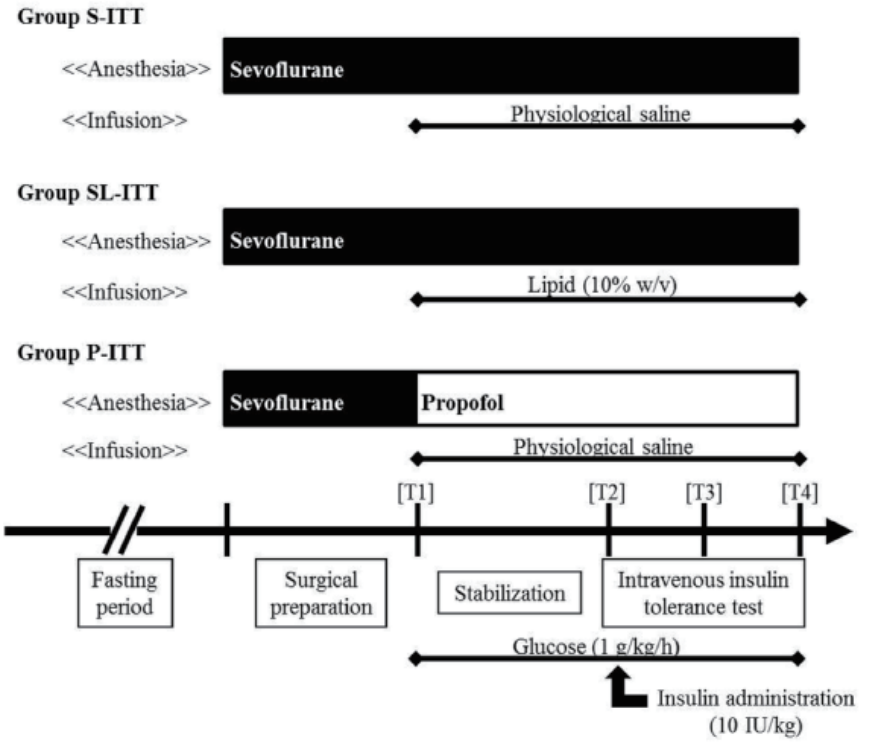

Figure 2. Experimental protocols for insulin tolerance tests (ITT). Another set of 21 rats underwent surgical preparation under sevoflurane anesthesia. Rats were assigned to 3 groups: groups S-ITT, SL-ITT and P-ITT. Immediately after surgical preparation, all rats were administered glucose by continuous infusion. Sevoflurane anesthesia was continued in groups S-ITT and SL-ITT. Physiological saline was administered intravenously in group S-ITT, while 10% w/v lipid was administered intravenously in group SL-ITT. Sevoflurane administration was discontinued, and instead propofol solution was administered intravenously in group P-ITT. After a 30-min stabilization period, the insulin tolerance test was performed. Hemodynamic variables were recorded, and arterial blood was sampled, immediately after surgical preparation (T1), immediately before (T2), and at 15 min (T3) and 30 min (T4) after insulin administration.

Table 1. Hemodynamic parameters during intravenous glucose tolerance tests in groups S-IVGTT, SL-IVGTT, and P-IVGTT

Items	T1	T2	T3	T4
Mean arterial blood pressure (mmHg)				
S-IVGTT	90 ± 19	81 ± 13	85 ± 7	67 ± 17
SL-IVTT	89 ± 6	90 ± 6	90 ± 9	74 ± 9
P-IVGTT	85 ± 11	111 ± 25*	93 ± 26	66 ± 33
Heart rate (beats/min)				
S-IVGTT	367 ± 21	399 ± 24	386 ± 28	372 ± 33
SL-IVGTT	380 ± 37	410 ± 38	390 ± 35	388 ± 32
P-IVGTT	375 ± 41	408 ± 53	372 ± 33	352 ± 29

Data are shown as means ± S.D. T1: just after surgical preparation. T2: just before glucose administration. T3: 15 min after glucose administration. T4: 30 min after glucose administration. Two-way repeated-measures ANOVA detected a significant difference among the three groups in the time course of MAP, but not in the time course of HR. *: adjusted $p < 0.05$ *versus* group S-IVGTT at the same time point, one-way ANOVA with the Bonferroni-Dunn test.

2.6. *Statistics*

Data were statistically analyzed using JMP Pro version 10.0.2. (SAS Institute, Cary, NC, USA). Parametric data are shown as means ± S.D. Serial data were compared among three groups using two-way repeated-measures analysis of variance (ANOVA) with group and time points as the factors; statistical significance was set at $p < 0.05$. Sphericity was checked using Mauchly's test; statistical significance was set at $p < 0.05$. When sphericity was not met, the Greenhouse-Geisser correction was applied; statistical significance was set at an adjusted $p < 0.05$. Parametric data were compared among three groups at each time point using one-way ANOVA; statistical significance was set at $p < 0.05$. When a significant difference was noted, the Bonferroni-Dunn test was applied for multiple comparisons; statistical significance was set at an adjusted $p < 0.05$.

Insulin and TNF-α levels in plasma and QUICKI are shown as medians [25th and 75th percentiles]. Non-parametric data at each time point were compared among three groups using the Kruskal-Wallis test; statistical significance was set at $p < 0.05$. When a significant difference was detected, the Steel-Dwass test was used for multiple comparisons; statistical significance was set at an adjusted $p < 0.05$.

3. Results

3.1. *IVGTT results*

The weights of the rats in groups S-IVGTT, SL-IVGTT, and P-IVGTT did not differ significantly: 273 ± 22, 271 ± 18, and 287 ± 26 g, respectively.

Table 1 shows the time course of the hemodynamic parameters during IVGTT in groups S-IVGTT, SL-IVGTT, and P-IVGTT. There was a significant difference in the time course of MAP among the three groups ($p = 0.0052$). MAP differed significantly among the three groups at T2 ($p = 0.0075$); group P-IVGTT showed significantly higher MAP than group S-IVGTT (adjusted $p = 0.0072$). There was no significant difference in the time course of HR among the three groups.

Table 2. Changes in blood glucose levels during intravenous glucose tolerance tests in groups S-IVGTT, SL-IVGTT, and P-IVGT

Items	Blood glucose levels (mg/dL)				AUC [T2-T4] (min•mg/dL)
	T1	T2	T3	T4	
S-IVGTT	79 ± 19	74 ± 17	246 ± 13	170 ± 15#	3301 ± 470
SL-IVGTT	87 ± 15	70 ± 9	217 ± 25	144 ± 22*	2763 ± 471
P-IVGTT	94 ± 18	53 ± 17*	196 ± 25*	113 ± 13*#	2601 ± 301*

Data are shown as means ± S.D. AUC [T2-T4]: the area under the time-response curve of blood glucose levels during the intravenous glucose tolerance test above the blood glucose level at T2 in each rat. T1: just after surgical preparation. T2: just before glucose administration. T3: 15 min after glucose administration. T4: 30 min after glucose administration. Two-way repeated-measures ANOVA with Greenhouse-Geisser correction detected a significant difference among the three groups in the time course of blood glucose levels. *: adjusted $p < 0.05$ versus group S-IVGTT at the same time point, one-way ANOVA with the Bonferroni-Dunn test. #: adjusted $p < 0.05$ versus group SL-IVGTT at the same time point, one-way ANOVA with the Bonferroni-Dunn test.

Table 2 shows the time course of blood glucose levels during the IVGTT in groups S-IVGTT, SL-IVGTT, and P-IVGTT. There was a significant difference in the time course of blood glucose levels among the three groups (adjusted $p < 0.0001$). Blood glucose levels differed significantly among the three groups at T2, T3, and T4 ($p = 0.0358$, $= 0.0020$ and < 0.0001, respectively). Group P-IVGTT showed significantly lower blood glucose levels at T2 and T3 than group S-IVGTT (adjusted $p = 0.0480$ and $p = 0.0015$, respectively). Groups SL-IVGTT and P-IVGTT showed significantly lower blood glucose levels at T4 than group S-IVGTT (adjusted $p = 0.0376$ and < 0.0001, respectively), and when compared to group SL-IVGTT, group P-IVGTT showed significantly lower blood glucose levels (adjusted $p = 0.0112$). AUC [T2-T4] differed significantly among the three groups ($p = 0.0164$). Group P-IVGTT showed significantly lower AUC [T2-T4] than group S-IVGTT (adjusted $p = 0.0195$).

Table 3 shows the time course of blood β-OHB levels during the IVGTT in groups S-IVGTT, SL-IVGTT, and P-IVGTT. There was a significant difference in the time

course of blood β-OHB levels among the three groups (adjusted $p < 0.0001$). Blood β-OHB levels differed significantly at T2, T3, and T4 among the three groups ($p = 0.0073$, < 0.0001, and < 0.0001, respectively). Group P-IVGTT showed significantly lower blood β-OHB levels at T2 than group SL-IVGTT (adjusted $p = 0.0066$). Group SL-IVGTT showed significantly higher blood β-OHB levels at T3 than groups S-IVGTT and P-IVGTT (adjusted $p < 0.0001$ and $= 0.0001$, respectively). Groups SL-IVGTT and P-IVGTT showed significantly higher blood β-OHB levels at T4 than group S-IVGTT (adjusted $p < 0.0001$ and $= 0.0001$, respectively), and when compared to group SL-IVGTT, group P-IVGTT showed significantly lower blood β-OHB levels (adjusted $p = 0.0283$, respectively).

Table 3. Changes in blood β-hydroxybutyrate levels during intravenous glucose tolerance tests in groups S-IVGTT, SL-IVGTT, and P-IVGTT

Items	T1	T2	T3	T4
Blood glucose levels (mg/dL)				
S-IVGTT	1.7 ± 0.6	2.1 ± 0.9	0.7 ± 0.5#	0.1 ± 0.1#
SL-IVGTT	1.8 ± 0.5	3.0 ± 0.5	2.3 ± 0.5*	1.5 ± 0.4*
P-IVGTT	1.5 ± 0.6	1.7 ± 0.6#	1.1 ± 0.5#	0.9 ± 0.4*#

Data are shown as means ± SD. T1: just after surgical preparation. T2: just before glucose administration. T3: 15 min after glucose administration. T4: 30 min after glucose administration. Two-way repeated-measures ANOVA with Greenhouse-Geisser correction detected a significant difference among the three groups in the time course of blood β-hydroxybutyrate levels. *: adjusted $p < 0.05$ versus group S-IVGTT at the same time point, one-way ANOVA with the Bonferroni-Dunn test. #: adjusted $p < 0.05$ versus group SL-IVGTT at the same time point, one-way ANOVA with the Bonferroni-Dunn test.

Table 4 shows the time course of plasma insulin levels during the IVGTT in groups S-IVGTT, SL-IVGTT, and P-IVGTT. Plasma insulin levels differed significantly among the three groups at T2, T3, and T4 ($p = 0.0001$, $p = 0.0001$, and $p = 0.0002$, respectively). Groups SL-IVGTT and P-IVGTT showed significantly higher plasma insulin levels at T2, T3, and T4 than group S-IVGTT (adjusted $p = 0.0061$ in all comparisons), and when compared to group SL-IVGTT, group P-IVGTT showed significantly higher plasma insulin levels at T2, T3, and T4 (adjusted $p = 0.0061$, $= 0.0061$, and $= 0.0137$, respectively).

QUICKI at T1 in groups S-IVGTT, SL-IVGTT, and P-IVGTT was 0.338 [0.309, 0.346], 0.315 [0.304, 0.329], and 0.304 [0.283, 0.319], respectively; QUICKI at T1 did not differ significantly among the three groups. QUICKI at T2 in groups S-IVGTT, SL-IVGTT, and P-IVGTT was 0.345 [0.310, 0.350], 0.253 [0.251, 0.257], and 0.241 [0.228, 0.253], respectively; QUICKI at T2 differed significantly among the three groups ($p = 0.0005$). Groups SL-IVGTT and P-IVGTT showed significantly lower QUICKI at T2 (adjusted $p = 0.0061$ and $p = 0.0061$, respectively), whereas QUICKI at T2 was similar between groups SL-IVGTT and P-IVGTT.

3.2. *ITT results*

The weight of the rats did not differ significantly among the S-ITT, SL-ITT, and P-ITT groups: 287 ± 19, 278 ± 14, and 291 ± 12 g, respectively.

Table 5 shows the time course of hemodynamic parameters during the ITT in groups S-ITT, SL-ITT, and

Table 4. Changes in plasma insulin levels during intravenous glucose tolerance tests in groups S-IVGTT, SL-IVGTT, and P-IVGTT

Items	T1	T2	T3	T4
Plasma insulin levels (μIU/mL)				
S-IVGTT	13 [12, 16]	12 [12, 17]§	122 [102, 251]§	44 [30, 75]§
SL-IVGTT	18 [14, 19]	122 [118, 131]†	538 [503, 650]†	300 [168, 420]†
P-IVGTT	20 [18, 35]	259 [249, 378]†§	3683 [2372, 4853]†§	2531 [702, 3447]†§

Data are shown as medians [25th, 75th percentiles]. T1: just after surgical preparation. T2: just before glucose administration. T3: 15 min after glucose administration. T4: 30 min after glucose administration. †: adjusted $p < 0.05$ versus group S-IVGTT at the same time point, Kruskal-Wallis test with the Steel-Dwass test. §: adjusted $p < 0.05$ *versus* group SL-IVGTT at the same time point, Kruskal-Wallis test with the Steel-Dwass test.

Table 5. Hemodynamic parameters during insulin tolerance tests in groups S-ITT, SL-ITT, and P-ITT

Items	T1	T2	T3	T4
Mean arterial blood pressure (mmHg)				
S-ITT	90 ± 13	95 ± 19	81 ± 17	69 ± 9
SL-ITT	92 ± 25	99 ± 9	78 ± 19	71 ± 14
P-ITT	82 ± 12	125 ± 14*#	96 ± 29	71 ± 33
Heart rate (beats/min)				
S-ITT	371 ± 23	408 ± 34	401 ± 26	382 ± 25
SL-ITT	369 ± 21	379 ± 34	371 ± 42	375 ± 31
P-ITT	346 ± 46	393 ± 41	377 ± 40	350 ± 46

Data are shown as means ± SD. T1: just after surgical preparation. T2: just before insulin administration. T3: 15 min after insulin administration. T4: 30 min after insulin administration. Two-way repeated-measures ANOVA detected a significant difference among the three groups in the time course of MAP, but not in the time course of HR. *: adjusted $p < 0.05$ versus group S-ITT at the same time point, one-way ANOVA with the Bonferroni-Dunn test. #: adjusted $p < 0.05$ versus group SL-ITT at the same time point, one-way ANOVA with the Bonferroni-Dunn test.

P-ITT. There was a significant difference in the time course of MAP among the three groups ($p = 0.0272$). MAP differed significantly among the three groups at T2 ($p = 0.0017$); group P-ITT showed significantly higher MAP than groups S-ITT and SL-ITT (adjusted $p = 0.0072$ and $= 0.0093$, respectively). There was no significant difference in the time course of HR among the three groups.

Table 6 shows the time course of blood glucose levels during the ITT in groups S-ITT, SL-ITT, and P-ITT. There was a significant difference in the time course of blood glucose levels among the three groups (adjusted $p < 0.0001$). Blood glucose levels differed significantly among the three groups at T2 and T4 ($p = 0.0020$ and $p = 0.0032$, respectively). Group P-ITT showed significantly lower blood glucose levels at T2 and significantly higher blood glucose levels at T4 than group S-ITT (adjusted p = 0.0015 and p = 0.0027, respectively). Δglucose [T2-T4] differed significantly among the three groups ($p < 0.0001$). Groups SL-ITT and P-ITT showed significantly less decreases in blood glucose levels after insulin administration than group S-ITT (adjusted $p = 0.0064$ and $p = 0.0001$, respectively).

Table 7 shows the time course of plasma TNF-α levels during the ITT in groups S-ITT, SL-ITT, and P-ITT. TNF-α was undetectable at T1 in all rats in the three groups. TNF-α was detected at T2 in all rats in groups SL-ITT and P-ITT, but not detected in any rats in group S-ITT. TNF-α was detected at T3 in 5 of 7 rats in group SL-ITT and in all rats in group P-ITT, but not detected in any rats in group S-ITT. TNF-α was detected at T4 in 1 of 7 rats in group S-ITT, in 4 of 7 rats in group SL-ITT, and in 6 of 7 rats in group P-ITT. Plasma TNF-α levels differed significantly among the three groups at T2, T3, and T4 ($p = 0.0009$, $= 0.0022$ and $= 0.0107$, respectively). Groups SL-ITT and P-ITT showed significantly higher plasma TNF-α levels than group S-ITT at T2 (adjusted $p = 0.0030$ and $= 0.0030$, respectively) and at T3 (adjusted $p = 0.0305$ and $p = 0.0030$, respectively). Group P-ITT showed significantly higher plasma TNF-α levels than group S-ITT at T4 (adjusted $p = 0.0063$).

Table 6. Changes in blood glucose levels during insulin tolerance tests in groups S-ITT, SL-ITT, and P-ITT

Items	Blood glucose levels (mg/dL)				Δglucose [T2-T4](mg/dL)
	T1	T2	T3	T4	
S-ITT	80 ± 12	167 ± 21	110 ± 12	95 ± 10	-72 ± 29#
SL-ITT	79 ± 17	145 ± 8	122 ± 14	130 ± 17	-15 ± 17*
P-ITT	91 ± 18	131 ± 17*	124 ± 23	151 ± 41*	21 ± 31*

Data are shown as means ± SD. Δglucose [T2-T4]: the changes in blood glucose levels during the insulin tolerance test. T1: just after surgical preparation. T2: just before insulin administration. T3: 15 min after insulin administration. T4: 30 min after insulin administration. Two-way repeated-measures ANOVA with Greenhouse-Geisser correction detected a significant difference among the three groups in the time course of blood glucose levels. *: adjusted $p < 0.05$ versus group S-ITT at the same time point, one-way ANOVA with the Bonferroni-Dunn test. #: adjusted $p < 0.05$ versus group SL-ITT at the same time point, one-way ANOVA with the Bonferroni-Dunn test.

4. Discussion

Based on the glucose levels and the changes in blood glucose levels (*i.e.*, AUC[T2-T4]) in groups S-IVGTT, SL-IVGTT and P-IVGTT, we consider that groups SL-IVGTT and P-IVGTT utilized larger amounts of glucose during the IVGTT than group S-IVGTT. However, groups SL-IVGTT and P-IVGTT showed significantly higher β-OHB levels during the IVGTT than group S-IVGTT. In addition, blood β-OHB levels during the IVGTT were significantly higher in group SL-IVGTT than in group P-IVGTT. Blood β-OHB levels correlate with the amount of gluconeogenesis *via* lipolysis (*i.e.*, fat catabolism). A recent clinical study (*16*) reported that glucose administration during surgery under sevoflurane anesthesia significantly suppresses lipolysis. Consistent with this finding, blood β-OHB levels decreased after glucose administration in group S-IVGTT in the present study. Therefore, exogenous lipid was probably utilized as an energy substrate in groups SL-IVGTT and P-IVGTT. It appears that an acute lipid load increases gluconeogenesis *via* lipolysis under sevoflurane anesthesia. Furthermore, the amount of exogenous lipid utilized as an energy substrate is larger under sevoflurane anesthesia than under propofol anesthesia. Taken together, these findings indicate that lipid metabolism is involved in the mechanisms underlying the different effects of sevoflurane anesthesia and propofol anesthesia on glucose utilization.

Insulin secretion is considered to predominantly regulate glucose utilization. Volatile anesthetics, such as sevoflurane, attenuate insulin secretion by activating

Table 7. Changes in plasma tumor necrosis factor-α levels during insulin tolerance tests in groups S-ITT, SL-ITT, and P-ITT

Items	T1	T2	T3	T4
Plasma tumor necrosis factor-α levels (pg/mL)				
S-ITT	0 [0, 0]	0 [0, 0]§	0 [0, 0]§	0 [0, 0]
SL-ITT	0 [0, 0]	1019 [747, 1386]†	604 [0, 1332]†	0 [0, 1207]
P-ITT	0 [0, 0]	1099 [819, 1954]†	1166 [667, 1707]†	646 [290, 730]†

Data are shown as medians [25th, 75th percentiles]. T1: just after surgical preparation. T2: just before insulin administration. T3: 15 min after insulin administration. T4: 30 min after insulin administration. †: adjusted $p < 0.05$ versus group S-ITT at the same time point, Kruskal-Wallis test with the Steel-Dwass test. §: adjusted $p < 0.05$ versus group SL-ITT at the same time point, Kruskal-Wallis test with the Steel-Dwass test.

adenosine triphosphate-sensitive potassium channels in β-islet cells (*2-5*). We previously found that propofol anesthesia enhances insulin secretion in rats (*6,7*). Groups SL-IVGTT and P-IVGTT showed significantly higher plasma insulin levels during IVGTT than group S-IVGTT. Interestingly, plasma insulin levels during IVGTT were significantly higher in group P-IVGTT than in group SL-IVGTT. These results suggest that an acute lipid load enhances insulin secretion under sevoflurane anesthesia by stimulating gluconeogenesis *via* lipolysis, and that insulin secretion can be additionally increased by propofol itself.

Insulin sensitivity is also considered to be a factor that regulates glucose utilization. Groups SL-IVGTT and P-IVGTT showed significantly lower QUICKI at T2 than group S-IVGTT, indicating insulin resistance in groups SL-IVGTT and P-IVGTT. An acute lipid load impairs insulin sensitivity (*8-11*), suggesting that lipid metabolism is involved in the regulation of insulin sensitivity. Cytokines and hormones derived from adipose tissues, such as TNF-α, regulate insulin sensitivity (*17,18*). The increase in plasma TNF-α levels associates with insulin resistance (*17,18*). Therefore, plasma TNF-α levels were measured during the ITT to further determine the mechanism underlying the insulin resistance in groups SL-IVGTT and P-IVGTT.

The decreases in blood glucose levels after insulin administration were significantly less in groups SL-ITT and P-ITT than in group S-ITT, reflecting insulin resistance in groups SL-ITT and P-ITT. There was no significant difference in the decreases in blood glucose levels after insulin administration between groups SL-ITT and P-ITT. Thus, it appears that an acute lipid load exaggerates insulin resistance under propofol anesthesia, while propofol does not.

Groups SL-ITT and P-ITT showed significantly higher plasma TNF-α levels during the ITT than group S-ITT. Therefore, an acute lipid load might increase TNF-α secretion from adipose tissues, leading to the insulin resistance observed in the present study. Further investigations are required to elucidate whether TNF-α is the main cause of the observed insulin resistance under propofol anesthesia, which is probably exaggerated by the acute lipid load.

Blood glucose levels should be appropriately controlled in patients undergoing surgery, because hyperglycemia is considered an independent risk factor for postoperative morbidity and mortality (*19-21*). Therefore, the significantly lower blood glucose levels under propofol anesthesia may reflect the possible advantageous effects of propofol anesthesia. On the other hand, the observed insulin resistance can be interpreted as a disadvantageous effect of propofol anesthesia on intraoperative glycemic control. The present findings are difficult to extrapolate to clinical practice, because the dose of propofol administered to rats is much larger than that administered to patients in clinical settings; the larger dose of propofol administration is accompanied by a larger acute lipid load. However, the results of the present study suggest that the effects of propofol anesthesia on insulin secretion, as well as insulin sensitivity, in clinical settings are worthy of further investigation.

This study has two major limitations. One is that all rats were anesthetized with sevoflurane for surgical preparation, and, thus, some residual effects might have altered glucose metabolism in groups P-IVGTT and P-ITT. The other is that the time course of hemodynamics differed significantly among groups S-IVGTT, SL-IVGTT, and P-IVGTT and among groups S-ITT, SL-ITT, and P-ITT. We previously reported that rats under propofol anesthesia at the same dose applied in the present study showed no changes in blood glucose levels during sigmoid colostomy (*1*), suggesting that propofol anesthesia is enough to suppress endocrine/metabolic responses to surgical stress. We did not measure plasma catecholamine levels. It is, therefore, difficult to estimate sympathetic nervous system activity during the experiments in rats used in the present study. Sympathetic nervous system activity is considered to modify glucose metabolism, and, thus, the possible impact of a significant difference in hemodynamics on glucose metabolism cannot be neglected.

In summary, propofol anesthesia enhances insulin secretion and concomitantly exaggerates insulin resistance compared with sevoflurane anesthesia. Propofol itself seemed to be the main cause of hyperinsulinemia rather than the acute lipid load, and insulin resistance was mainly attributed to the acute lipid load, which might be associated with the systemic release of TNF-α.

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