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Title

Involvement of adenosine triphosphate-sensitive potassium channels in the different effects of sevoflurane and propofol on glucose metabolism in fed rats

Short Title
Anesthetics, K_{ATP} channels and glucose

1. Takayuki Kitamura

- Title: M.D.
- Affiliation: Department of anesthesiology, Faculty of Medicine, The University of Tokyo
- Email: tyy-kitamura@m7.dion.ne.jp
- Conflict of Interest: None
- Contribution: Study design, Conduct of study, Data analysis and Manuscript preparation. Takayuki Kitamura attests to the integrity of the original data and the analysis.

2. Kanako Sato

- Title: M.D.
- Affiliation: Department of anesthesiology, Faculty of Medicine, The University of Tokyo
- Email: satoka-tky@umin.ac.jp
- Conflict of Interest: None
- Contribution: Study design, Conduct of study, Data analysis and Manuscript preparation. Kanako Sato attests to the integrity of the original data and the analysis.

3. Gaku Kawamura

- Title: M.D.
- Affiliation: Department of anesthesiology, Faculty of Medicine, The University of Tokyo
- Email: kawamurag-ane@h.u-tokyo.ac.jp
- Conflict of Interest: None
- Contribution: Study design, Conduct of study, Data analysis and Manuscript preparation. Gaku Kawamura attests to the integrity of the original data and the analysis.

4. Yoshitsugu Yamada

- Title: M.D., Ph.D.
- Affiliation: Department of anesthesiology, Faculty of Medicine, The University of Tokyo
- Email: yamaday-ane@h.u-tokyo.ac.jp
- Conflict of Interest: None
- Contribution: Data analysis and Manuscript preparation.

Name of Department(s) and Institution(s)
Department of anesthesiology, Faculty of Medicine, The University of Tokyo

7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan 113-8655

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Tel: +81-3-5800-8668, Fax: +81-3-5800-8938

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Corresponding Author: Takayuki Kitamura, M.D.

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Abstract

BACKGROUND: Recently, we reported marked differences in the effects of sevoflurane and propofol on glucose metabolism; glucose use is impaired by sevoflurane, but not by propofol. Opening of adenosine triphosphate-sensitive potassium channels (K_{ATP}-channels) in β-islet cells attenuates insulin secretion, while inhibition of K_{ATP}-channels in β-islet cells increases insulin secretion. It is reported that volatile anesthetics open K_{ATP}-channels, whereas propofol inhibits K_{ATP}-channels. In this study, we examined the effects of sevoflurane and propofol on glucose metabolism under normovolemic and hypovolemic conditions, focusing on insulin secretion.

METHODS: Anesthesia was induced with sevoflurane (3% in 1 l/min oxygen) in all rats. After surgical preparation, rats were assigned to two groups. Anesthesia was maintained with sevoflurane (2% in 1 l/min oxygen) in the first group, and with propofol (a bolus dose of 30 mg/kg followed by continuous infusion at a rate of 30 $mg \cdot kg^{-1} \cdot h^{-1}$) in the second group. Each group was divided into three subgroups: rats without pretreatment, rats pretreated with glibenclamide, and rats pretreated with nicorandil. After a 30-min stabilization period, we withdrew 15 ml/kg of blood to induce hypovolemia. We evaluated glucose metabolism under both normovolemic and hypovolemic conditions by measuring blood glucose levels and plasma insulin levels.

RESULTS: Under both normovolemia and hypovolemia, glucose levels in rats anesthetized with sevoflurane were significantly higher than those in rats anesthetized with propofol, and insulin levels in rats anesthetized with sevoflurane were significantly lower than those in rats anesthetized with propofol. Glibenclamide, a K_{ATP}-channel inhibitor, significantly decreased glucose levels and significantly increased insulin levels under sevoflurane anesthesia, suggesting

that sevoflurane decreases insulin secretion by opening K_{ATP}-channels in β-islet cells. Glibenclamide significantly decreased glucose levels and significantly increased insulin levels under propofol anesthesia as well; however, insulin levels in rats pretreated with glibenclamide under propofol anesthesia were much higher than those in rats pretreated with glibenclamide under sevoflurane anesthesia. Furthermore, insulin levels in rats without pretreatment under propofol anesthesia seemed to be equal to or higher than those in rats pretreated with glibenclamide under sevoflurane anesthesia. These results suggest that there are marked differences in the effects of sevoflurane and propofol on insulin secretion regulated by K_{ATP}-channels in β-islet cells. Nicorandil, a K_{ATP}-channel opener, produced no significant effects on glucose metabolism under both sevoflurane and propofol anesthesia.

CONCLUSIONS: Insulin secretion regulated by K_{ATP}-channels in β-islet cells is involved, at least in part, in the different effects of sevoflurane and propofol on glucose metabolism.

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Introduction

Control of blood glucose levels is an important concern in the anesthetic management of patients undergoing surgery, since intra-operative hyperglycemia is an independent risk factor for mortality and morbidity related to surgery.[1-3] Both glucose use and glucose production are modified by surgical stress; impaired insulin secretion results in decreased glucose use, while elevated blood concentrations of catabolic hormones enhance glucose production.[4,5] Both sevoflurane, a volatile anesthetic, and propofol, an intravenous anesthetic, are popular agents used for maintenance of general anesthesia in clinical settings. Recently, we reported that the effect of sevoflurane on glucose metabolism under aerobic conditions is markedly different from that of propofol in fed rats; glucose use is significantly impaired by sevoflurane, but not by propofol.[6] Several studies have reported that volatile anesthetics impair insulin secretion.[5,7-10] Volatile anesthetics open adenosine triphosphate-sensitive potassium channels (K_{ATP}-channels),[11-13] whereas propofol inhibits K_{ATP}-channels.[14-16] K_{ATP}-channels in β-islet cells play important roles in insulin secretion; opening of K_{ATP}-channels in β-islet cells attenuates insulin secretion, while inhibition of K_{ATP}-channels in β-islet cells increases insulin secretion.[17] Both anaerobic glucose metabolism as well as aerobic glucose metabolism can occur in patients undergoing surgery. Oxygen demand/supply imbalance induced by severe hemorrhage exaggerates anaerobic glucose metabolism. We, thus, examined the effects of sevoflurane and propofol on glucose metabolism under normovolemic as well as hypovolemic conditions in fed rats, focusing on insulin secretion regulated by K_{ATP}-channels in β-islet cells.

Methods

Subjects

All experimental protocols were approved by the animal care committee of our institute. We used 9- to 10-week-old, male, Sprague-Dawley rats (Nippon Bio-Supp. Center, Tokyo, Japan). 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 $_{PM}$). Food (24% protein, 5% fat, 6% ash, 3% fiber, 8% water and 54% nitrogen-free extract) and water were provided *ad libitum* until the experiments. All experiments were performed between 9 $_{AM}$ and 5 $_{PM}$. A heat lamp and a heating pad were used for the prevention of hypothermia during the experiments.

Experimental protocols

The experimental protocols are summarized in Figure 1. We used 42 rats in this study. Anesthesia for surgical preparation was provided with sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan). Sevoflurane (3% in 1 l/min oxygen) was administered via a tightly fitting mask for induction of anesthesia. All rats underwent tracheotomy and tracheal intubation. After tracheal intubation, sevoflurane (3% in 1 l/min oxygen) was administered via the tracheal tube and the lungs were mechanically ventilated. Tidal volume was set at 2.5 ml and respiratory rate was set at 60 breaths/min. A 19-gauge catheter was inserted into the right carotid artery and another 19-gauge catheter was inserted into the right jugular vein. All rats were administered 100 IU of heparin intravenously to maintain patency of the catheters. Immediately after surgical preparation, we recorded hemodynamic parameters and sampled 1 ml of arterial blood (T-1).

Rats were assigned to two groups (group S and group P). We continued sevoflurane administration to rats in group S (n=21); inhalational concentration of sevoflurane was changed

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from 3% to 2%, and physiological saline (a bolus dose of 3 ml/kg followed by continuous infusion at a rate of 3 $ml{\cdot}kg^{-1}{\cdot}h^{-1}$) was administered intravenously. In rats in group P (n=21), sevoflurane administration was discontinued and instead propofol solution with a concentration of 10 mg/ml (AstraZeneca K. K., Osaka, Japan) was administered intravenously, with a bolus dose of 30 mg/kg followed by continuous infusion at a rate of 30 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$. The doses of sevoflurane and propofol for maintenance of anesthesia were selected according to the protocol of our previous study.[6] At this time-point, each group was divided into three subgroups (i.e., 7 rats per subgroup). Rats assigned to group S[-] and group P[-] received no pretreatment. Rats assigned to group S[g] and group P[g] were pretreated with 0.5 mg/kg of glibenclamide (Sigma-Aldrich Japan, Tokyo, Japan), a K_{ATP}-channel inhibitor. Rats assigned to group S[n] and group P[n] were pretreated with 1 mg/kg of nicorandil (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan), a K_{ATP}-channel opener. Glibenclamide was dissolved in dimethyl sulphoxide (Sigma-Aldrich Japan) to a concentration of 1 mg/ml. Nicorandil was dissolved in physiological saline to a concentration of 2 mg/ml. Drugs for pretreatment were administered intravenously. To adjust total fluid load, rats in group S[-] and group P[-] were administered 0.5 ml/kg of physiological saline intravenously.

A 30-min stabilization period was allowed, following which we recorded hemodynamic parameters and sampled 1 ml of arterial blood (T-2). Then, we started to withdraw 15 ml/kg of blood via the arterial catheter at a rate of 3 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$. Immediately after the blood withdrawal, we once again recorded hemodynamic parameters and sampled 1 ml of arterial blood (T-3).

Measurements

The arterial catheter was connected to a low volume pressure transducer for monitoring mean arterial blood pressure (MAP) and heart rate (HR). Immediately after each blood sampling, blood

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lactate levels and blood glucose levels were measured using a blood gas analyzer (i-STAT 1 Analyzer; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan). Each blood sample was spun in a pre-refrigerated centrifuge (4°C) at 1000 × g for 15 min, and plasma was stored at -60°C. Plasma insulin levels were measured by enzyme-linked immunosorbent assay using AKRIN-010T (Shibayagi Co., Ltd., Gunma, Japan).

Statistical analysis

Data are shown as means ± SEM. Statistical analyses were performed using StatView version 5.0 (SAS Institute, Cary, NC) and JMP version 7.0.2. (SAS Institute). Homogeneity of variance was examined using Bartlett test. For comparisons of body weight and all experimental data at T-1 among all groups (i.e., six groups), we used one-way analysis of variance (ANOVA); statistical significance was set at $P < 0.05$. For overall comparisons of serial data within each group, we used one-way repeated measures ANOVA; statistical significance was set at $P < 0.05$. For overall comparisons of serial data between two groups (i.e., between groups S[-] and P[-]) and among three groups (i.e., among groups S[-], S[g] and S[n] and among groups P[-], P[g] and P[n]), we used two-way repeated measures ANOVA, with group and time-point as the factors; statistical significance was set at $P < 0.05$. We used Welch test for comparisons of blood lactate levels, blood glucose levels and plasma insulin levels at each time point between the two groups; statistical significance was set at $P < 0.05$. We used one-way ANOVA with Scheffé F test as a post hoc test for comparisons of blood glucose levels and plasma insulin levels at each time-point among the three groups; statistical significance was set at adjusted $P < 0.05$.

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Results

Hemodynamics

There were no significant differences in body weight among the six groups. The time required for surgical preparation was approximately 30 min in all rats. All rats in the six groups survived throughout the experimental period.

There were no significant differences in MAP at T-1 among the six groups. Figure 2A shows the time-course of MAP from T-1 to T-3 in groups S[-] and P[-]. Significant changes in MAP were observed in group S[-] ($P = 0.0027$, one-way repeated measures ANOVA). Significant changes in MAP were also observed in group P[-] ($P < 0.0001$, one-way repeated measures ANOVA). There were, however, no significant differences in the time-course of MAP between groups S[-] and P[-]. As shown in Figure 2B, there were no significant differences in the time-course of MAP among groups S[-], S[g] and S[n]. As shown in Figure 2C, there were no significant differences in the time-course of MAP among groups P[-], P[g] and P[n].

There were no significant differences in HR at T-1 among the six groups. The time-course of HR from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 3A. No significant changes in HR were observed in group S[-] over time. Significant changes in HR were observed in group P[-] ($P = 0.0022$, one-way repeated measures ANOVA). There were, however, no significant differences in the time-course of HR between groups S[-] and P[-]. As shown in Figure 3B, there were no significant differences in the time-course of HR among groups S[-], S[g] and S[n]. As shown in Figure 3C, there were no significant differences in the time-course of HR among groups P[-], P[g] and P[n].

Blood lactate levels

There were no significant differences in lactate levels at T-1 among the six groups. The time-course of lactate levels from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 4A. Significant changes in lactate levels were observed in group S[-] ($P = 0.0002$, one-way repeated measures ANOVA). Significant changes in lactate levels were also observed in group P[-] ($P < 0.0001$). There were significant differences in the time-course of lactate levels between groups S[-] and P[-] ($P = 0.0003$, two-way repeated measures ANOVA); lactate levels at T-3 in group P[-] were significantly higher than those in group S[-] ($P = 0.0158$, Welch test). As shown in Figure 4B, there were no significant differences in the time-course of lactate levels among groups S[-], S[g] and S[n]. As shown in Figure 4C, there were also no significant differences in the time-course of lactate levels among groups P[-], P[g] and P[n].

Blood glucose levels

There were no significant differences in glucose levels at T-1 among the six groups. The time-course of glucose levels from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 5A. No significant changes in glucose levels were observed in group S[-] over time. Significant changes in glucose levels were observed in group P[-] ($P < 0.0001$, one-way repeated measures ANOVA). There were significant differences in the time-course of glucose levels between groups S[-] and P[-] ($P = 0.0402$, two-way repeated measures ANOVA); glucose levels at T-2 and T-3 in group P[-] were significantly lower than those in group S[-] ($P < 0.0001$ and $P = 0.0002$, respectively, Welch test). As shown in Figure 5B, there were significant differences in the time-course of glucose levels among groups S[-], S[g] and S[n] ($P < 0.0001$, two-way repeated measures ANOVA); glucose levels at T-2 and T-3 in group S[g] were significantly lower than those in group S[-] (adjusted $P < 0.0001$ and adjusted $P < 0.0001$, respectively, Scheffé F test). As shown

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in Figure 5C, there were significant differences in the time-course of glucose levels among groups P[-], P[g] and P[n] (P = 0.0162, two-way repeated measures ANOVA); glucose levels at T-2 and T-3 in group P[g] were significantly lower than those in group P[-] (adjusted P = 0.0004 and adjusted P = 0.0225, respectively, Scheffé F test).

Plasma insulin levels

There were no significant differences in insulin levels at T-1 among the six groups. The time-course of insulin levels from T-1 to T-3 in groups S[-] and P[-] are shown in Figure 6A. No significant changes in insulin levels were observed in group S[-] over time. Significant changes in insulin levels were observed in group P[-] (P = 0.0020, one-way repeated measures ANOVA). There were significant differences in the time-course of insulin levels between groups S[-] and P[-] (P = 0.0007, two-way repeated measures ANOVA); insulin levels at T-2 and T-3 in group P[-] were significantly higher than those in group S[-] (P = 0.0087 and P = 0.0154, respectively, Welch test). As shown in Figure 6B, there were significant differences in the time-course of insulin levels among groups S[-], S[g] and S[n] (P < 0.0001, two-way repeated measures ANOVA); insulin levels at T-2 and T-3 in group S[g] were significantly higher than those in group S[-] (adjusted P = 0.0003 and adjusted P = 0.0021, respectively, Scheffé F test). As shown in Figure 6C, there were significant differences in the time-course of insulin levels among groups P[-], P[g] and P[n] (P < 0.0001, two-way repeated measures ANOVA); insulin levels at T-2 and T-3 in group P[g] were significantly higher than those in group P[-] (adjusted P < 0.0001 and adjusted P = 0.0011, respectively, Scheffé F test).

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Discussion

Blood glucose levels at T-2 in group S[-] were significantly higher than those in group P[-], suggesting significant differences in the effects of sevoflurane and propofol on glucose metabolism under normovolemic conditions. Blood glucose levels at T-3 in group S[-] were significantly higher than those in group P[-], suggesting significant differences in the effects of sevoflurane and propofol on glucose metabolism under hypovolemic conditions.

Recently, we reported that glucose use under aerobic condition in fed rats is significantly impaired by sevoflurane, but not by propofol.[6] Glucose use is affected by insulin secretion as well as insulin sensitivity. K_{ATP}-channels in β-islet cells play important roles in insulin secretion; insulin secretion is decreased by opening K_{ATP}-channels in β-islet cells, but is increased by inhibiting K_{ATP}-channels in β-islet cells.[17] K_{ATP}-channels consist of a pore-forming subunit (Kir6.1 or Kir6.2) and a regulatory subunit (sulfonylurea receptor; SUR1, SUR2A or SUR2B); SUR1 coupled with Kir6.2 (SUR1/Kir6.2) forms K_{ATP}-channels in β-islet cells, SUR2A coupled with Kir6.2 (SUR2A/Kir6.2) forms K_{ATP}-channels in cardiac myocytes, SUR2B coupled with Kir6.2 (SUR2B/Kir6.2) forms K_{ATP}-channels in nonvascular smooth muscle cells, and SUR2B coupled with Kir6.1 (SUR2B/Kir6.1) forms K_{ATP}-channels in vascular smooth muscle cells.[18-24] Glibenclamide, a K_{ATP}-channel inhibitor, has a high affinity for SUR1, SUR2A and SUR2B; however, nicorandil, a K_{ATP}-channel opener, has a high affinity for SUR2A and SUR2B, but not for SUR1.[22-24]

Several studies reported that volatile anesthetics impair insulin secretion.[5,7-10] Volatile anesthetics open K_{ATP}-channels,[11-13] and a recent study[25] reported that the opening effects of isoflurane on K_{ATP}-channels in β-islet cells contributed to attenuate insulin secretion, resulting in

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hyperglycemia. Plasma insulin levels at T-2 and T-3 in group S[-] were significantly lower than those in group P[-], implying that insulin secretion is involved, at least in part, in the different effects of sevoflurane and propofol on glucose metabolism under normovolemic as well as hypovolemic conditions. Glibenclamide significantly increased plasma insulin levels in rats under sevoflurane anesthesia, suggesting that sevoflurane decreases insulin secretion by opening K_{ATP}-channels in β-islet cells.

It was reported that propofol inhibited SUR1/Kir6.2, SUR2A/Kir6.2 and SUR2B/Kir6.2 expressed in COS-7 cells (African green monkey kidney cells), whereas propofol produced no significant effects on SUR2B/Kir6.1 expressed in COS-7 cells.[14] These results in *in vitro* study suggest the possible inhibitory effects of propofol on K_{ATP}-channels in β-islet cells; however, the effects of propofol, at the doses used in clinical settings, on insulin secretion regulated by K_{ATP}-channels in β-islet cells have not been elucidated. In group P[-], plasma insulin levels at T-2 were significantly higher than those at T-1, suggesting that propofol ameliorated the immediately preceding inhibitory effects of sevoflurane on insulin secretion. Glibenclamide significantly increased plasma insulin levels in rats under propofol anesthesia in this study. Plasma insulin levels in group P[g] (104.4±13.9 and 133.8±27.6 ng/ml at T-2 and T-3, respectively) were much higher than those in group S[g] (8.8±1.2 and 8.8±1.0 ng/ml at T-2 and T-3, respectively). In addition, plasma insulin levels in group P[-] (8.7±1.9 and 23.9±6.3 ng/ml at T-2 and T-3, respectively) seemed to be equal to or higher than those in group S[g]. Taken together, these results suggest that there are marked differences in the effects of sevoflurane and propofol on insulin secretion regulated by K_{ATP}-channels in β-islet cells. We suppose that there are two possibilities. First, propofol increases insulin secretion by inhibiting K_{ATP}-channels in β-islet cells; however, propofol cannot completely inhibit them at the dose tested in this study. Second,

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propofol produces no significant effects on insulin secretion regulated by K_{ATP}-channels in β-islet cells.

Hemorrhage shock causes cardiac dysfunction. A recent study[26] reported that the inhibition of K_{ATP}-channels in the cardiovascular system worsens hemorrhagic shock-induced myocardial ischemia, while the opening of K_{ATP}-channels in the cardiovascular system prevents the extension of hemorrhagic shock-induced myocardial ischemia. Changes in cardiac function may induce significant alterations to metabolism. We, thus, compared hemodynamics and glucose metabolism under hypovolemic conditions among rats without pretreatment, rats pretreated with glibenclamide and rats pretreated with nicorandil. There were no significant differences in hemodynamic parameters at T-3 among groups S[-], S[g] and S[n] as well as among groups P[-], P[g] and P[n]. Nicorandil produced no significant effects on glucose metabolism at T-3 under sevoflurane anesthesia as well as propofol anesthesia. We, therefore, believe that the significantly increased insulin secretion at T-3 in groups S[g] and P[g] reflected the effects of glibenclamide on K_{ATP}-channels in β-islet cells under sevoflurane anesthesia and propofol anesthesia, respectively.

The decrease in oxygen delivery related to severe hemorrhage exaggerates peripheral oxygen demand/supply imbalance, leading to anaerobic glucose metabolism and increases in blood lactate levels.[27,28] Severe, uncompensated hemorrhage may attenuate the clearance rate of lactate, since blood perfusion to major organs, such as the liver, as well as peripheral tissues is decreased.[29] Therefore, both the increased production and the decreased clearance of lactate are responsible for the increased blood lactate levels during hemorrhagic shock. We believe that induction of anaerobic glucose metabolism contributed to the significant increases in blood lactate levels under hypovolemic conditions in this study. Interestingly, blood lactate levels at T-

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3 in group P[-] were significantly higher than those in group S[-]. These results suggested that the increase in glucose use under hypovolemic conditions may lead to the enhancement of lactate production associated with anaerobic glucose metabolism, resulting in the significantly higher blood lactate levels.

We focused on insulin secretion to examine the different effects of sevoflurane and propofol on glucose metabolism in this study. Both insulin secretion and insulin sensitivity affect glucose use. Changes in both glucose use and glucose production are associated with stress-induced hyperglycemia. It is, therefore, necessary to examine the effects of the two anesthetics on insulin sensitivity and glucose production for further elucidation of their effects on glucose homeostasis. In this study, we used fed rats to avoid the possible effects of fasting on glucose metabolism; however, patients are usually made to fast prior to surgery in clinical settings. Thus, experiments using fasted animals are also required to elucidate the effects of the two anesthetics on glucose metabolism.

In conclusion, insulin secretion regulated by K_{ATP}-channels in β-islet cells is involved, at least in part, in the different effects of sevoflurane and propofol on glucose metabolism in fed rats.

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Figures and Illustrations

Figure 1

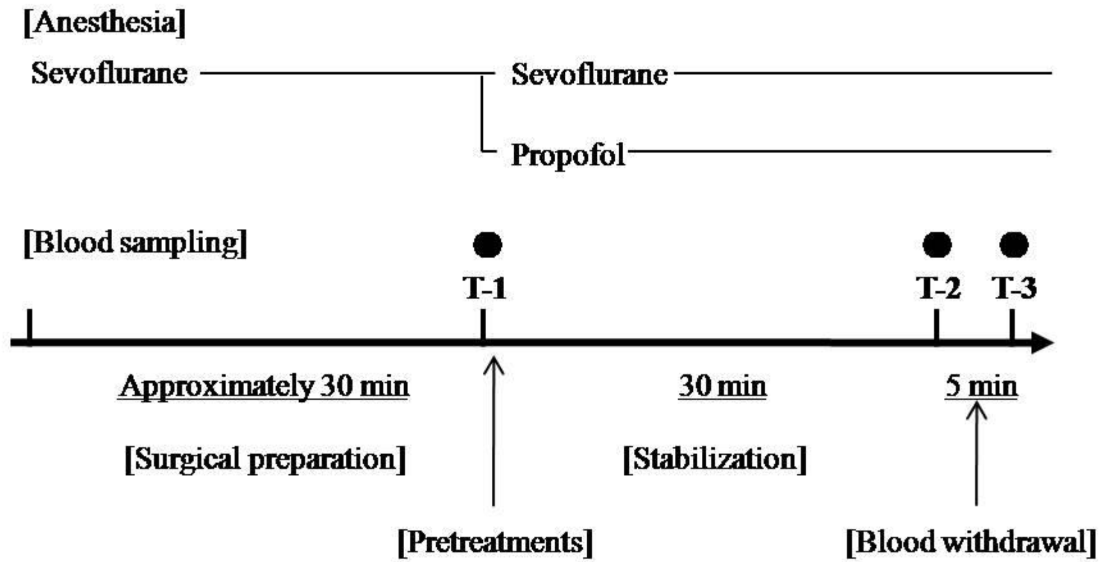

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Figure 2

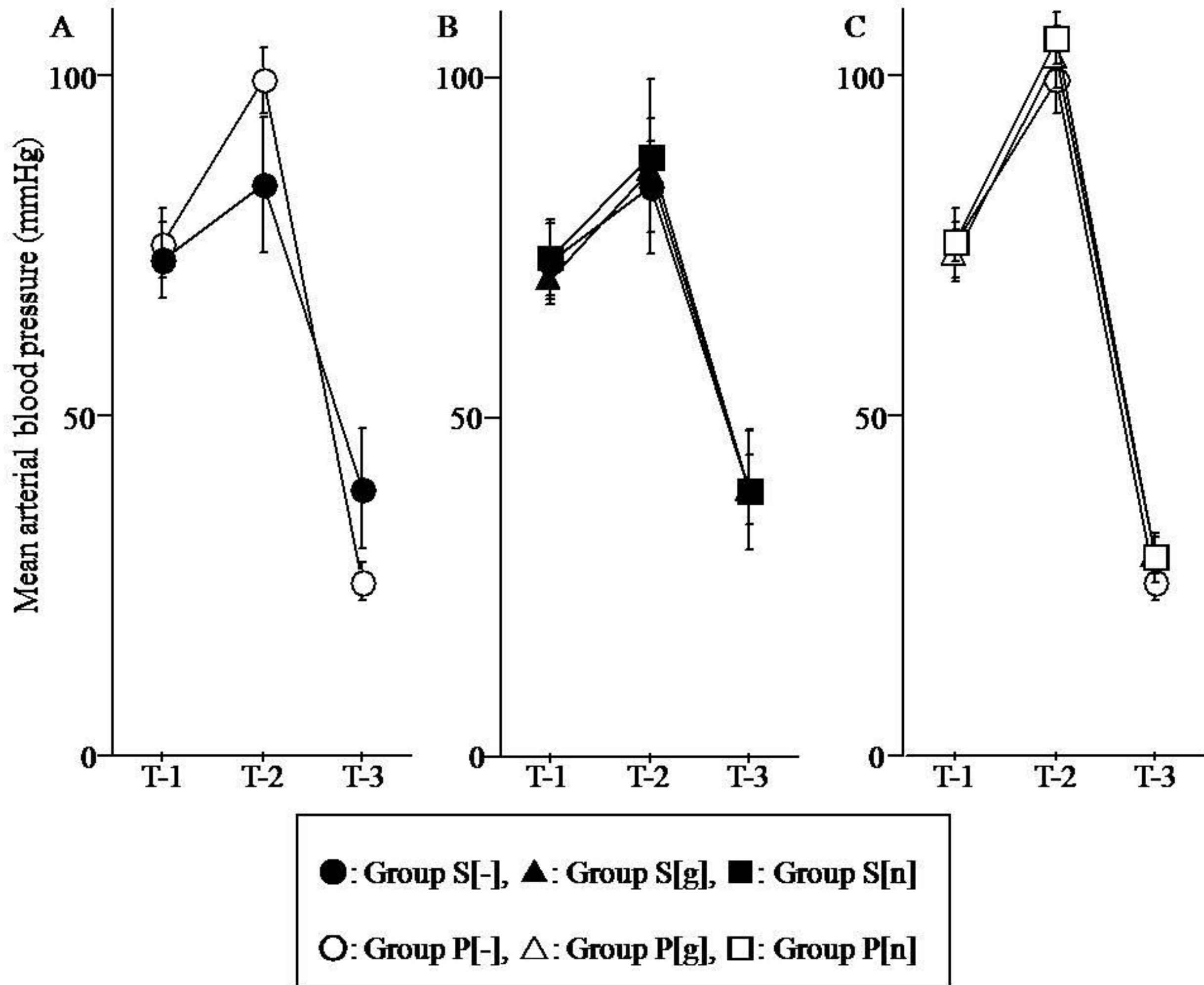

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Figure 3

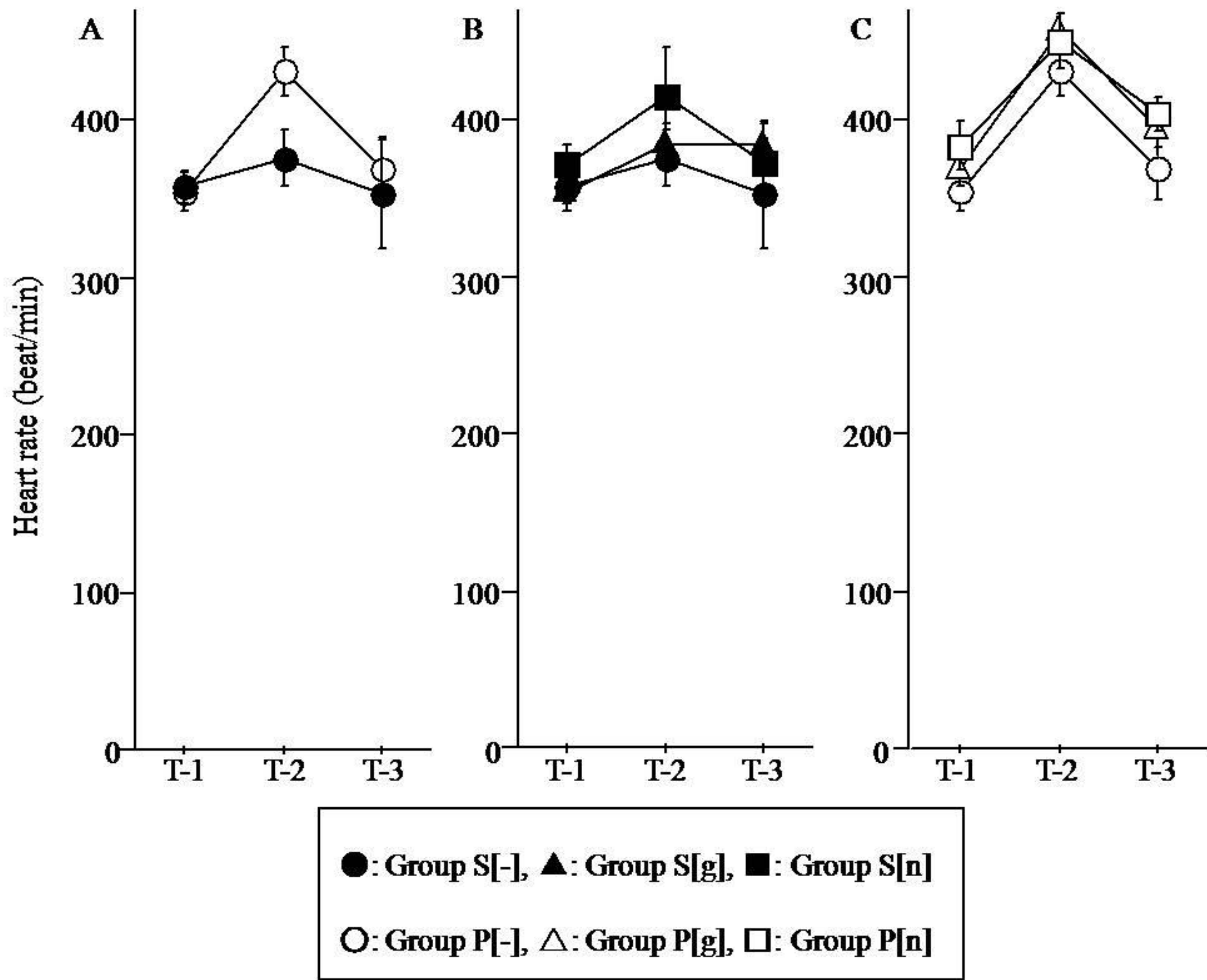

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Figure 4

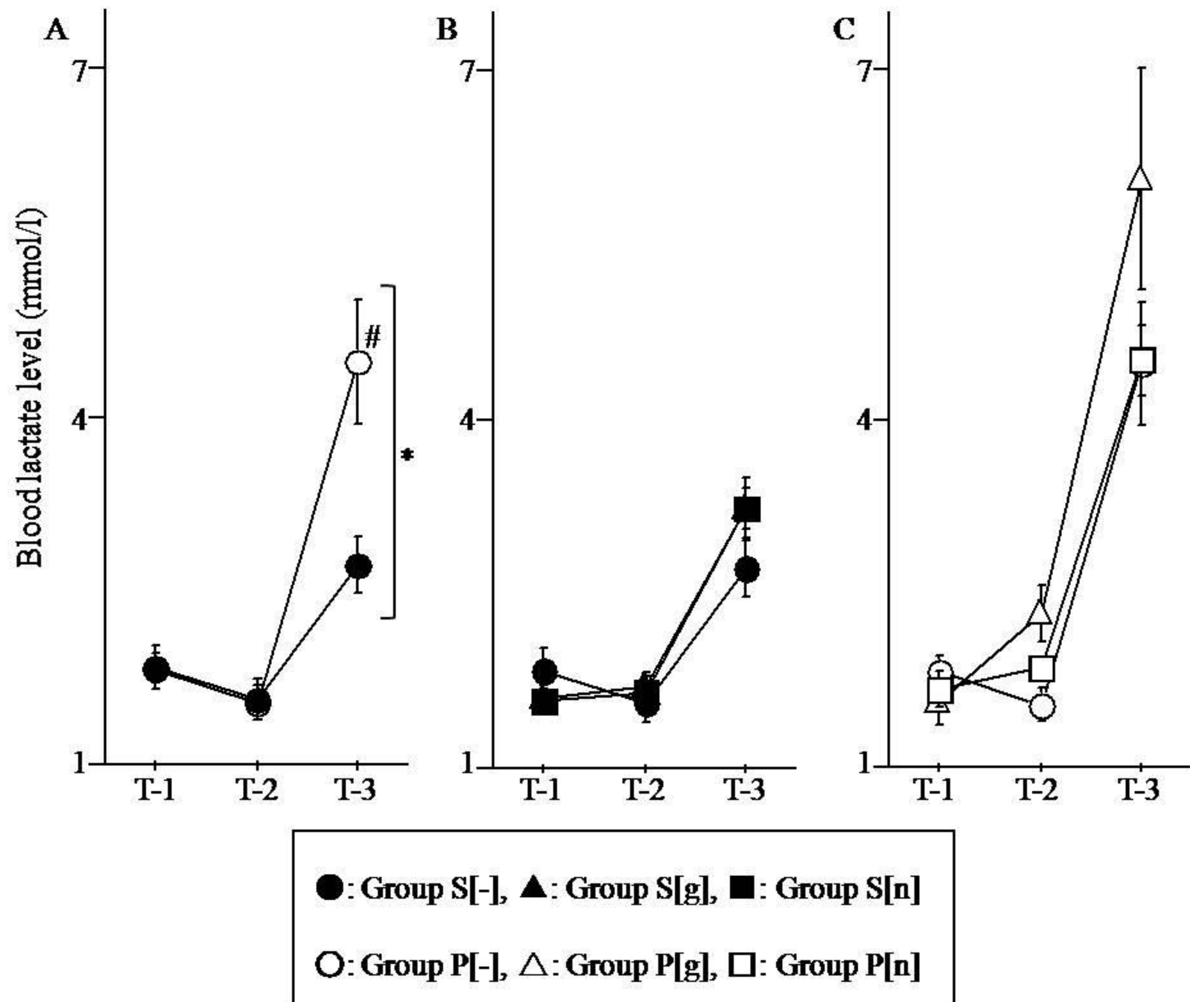

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Figure 5

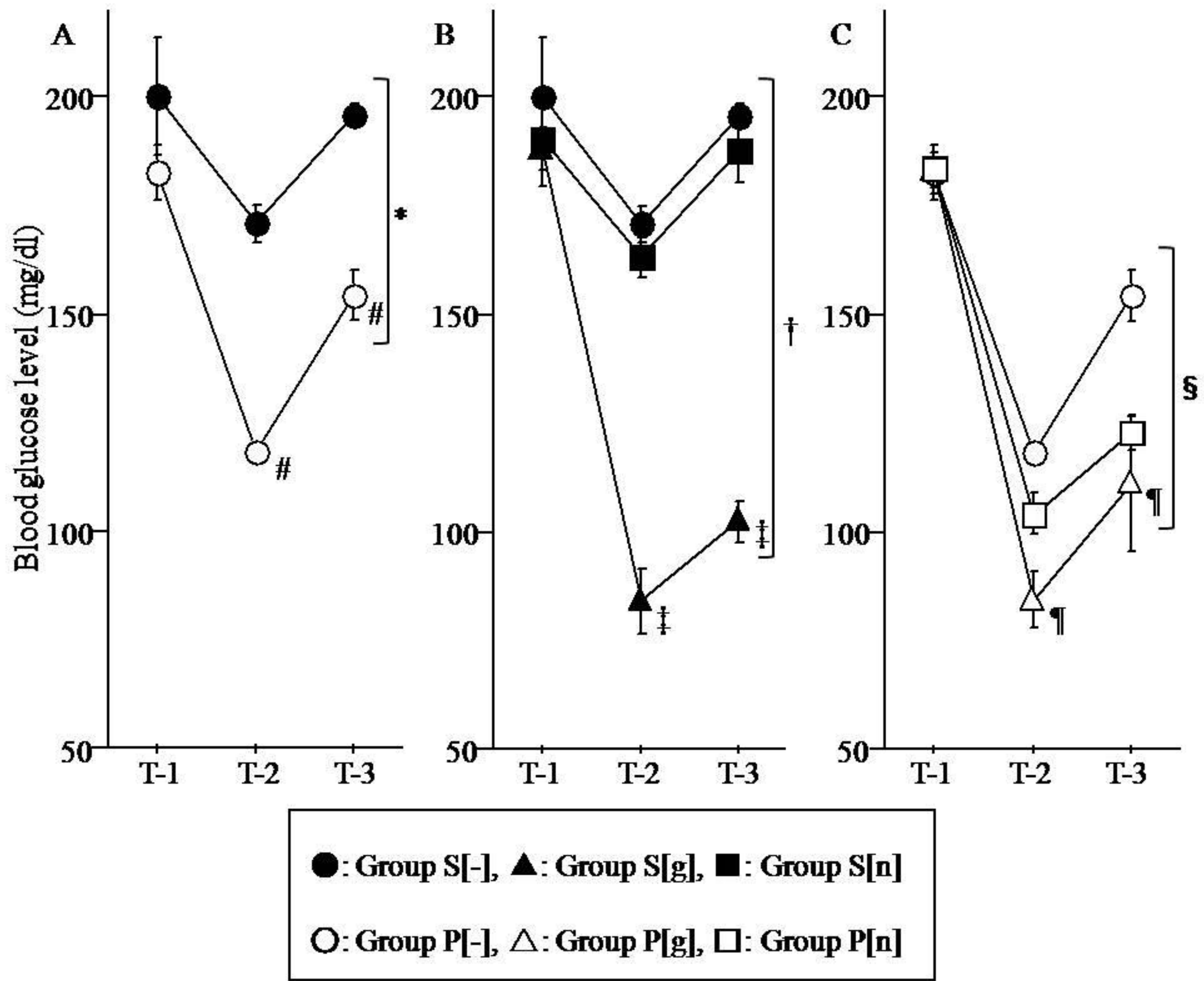

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Figure 6

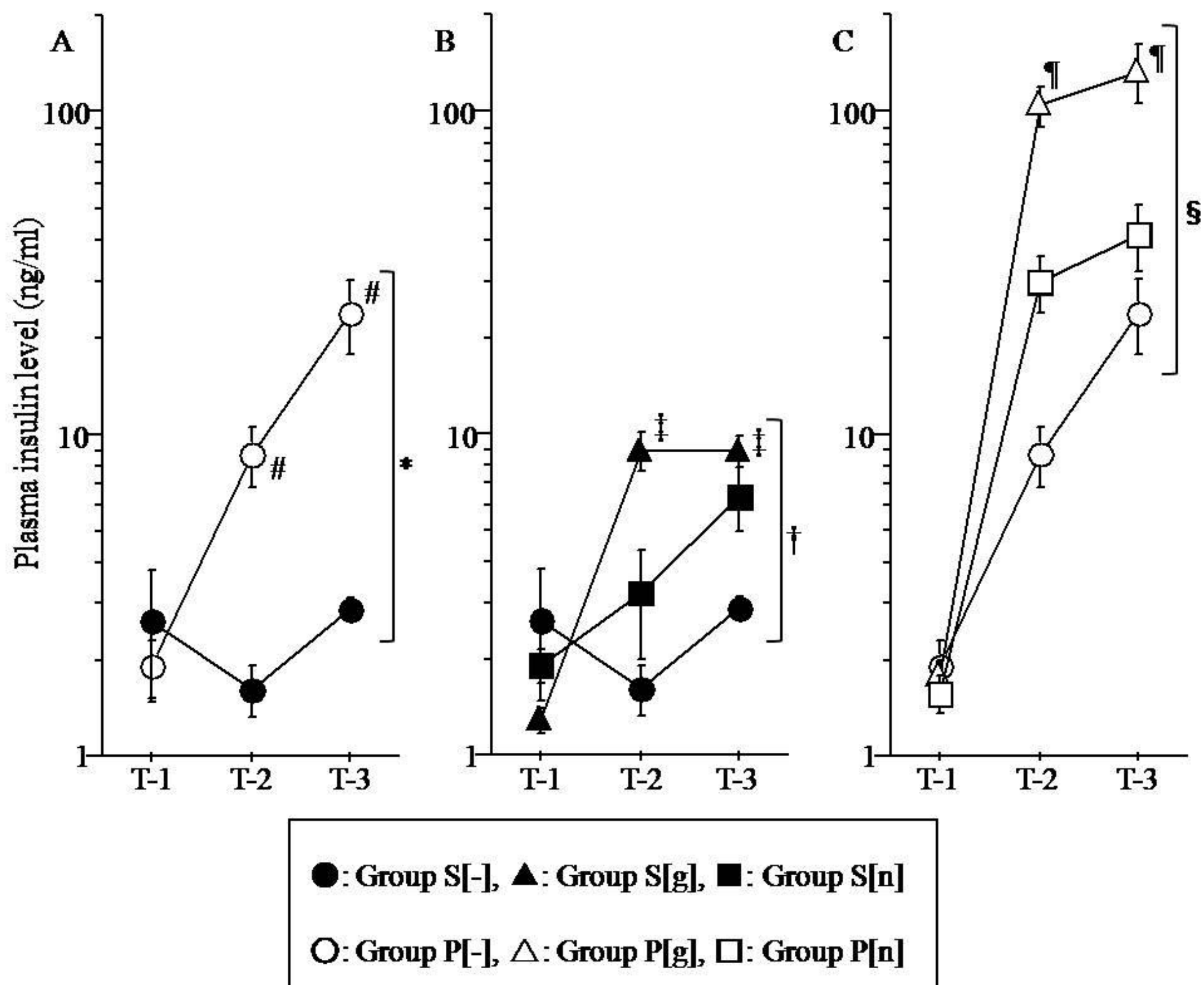

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Figure Legends

Figure 1

Experimental protocol. Surgical preparation was performed under sevoflurane anesthesia in all rats. After surgical preparation, anesthesia was maintained using either sevoflurane or propofol. Each group was divided into three subgroups: rats without pretreatment, rats pretreated with glibenclamide and rats pretreated with nicorandil. We started blood withdrawal at 30 min after the surgical preparation. We sampled arterial blood at T-1 (i.e., immediately after surgical preparation), T-2 (i.e., just prior to blood withdrawal) and T-3 (i.e., immediately after completion of blood withdrawal).

Figure 2

The time-course of mean arterial blood pressure (MAP). Panel-A shows the time-course of MAP in groups S[-] and P[-]. There were no significant differences in the time-course between the two groups. Panel-B shows the time-course of MAP in groups S[-], S[g] and S[n]. There were no significant differences in the time-course among the three groups. Panel-C shows the time-course of MAP in groups P[-], P[g] and P[n]. There were no significant differences in the time-course among the three groups.

Figure 3

The time-course of heart rate (HR). Panel-A shows the time-course of HR in groups S[-] and P[-]. There were no significant differences in the time-course between the two groups. Panel-B shows the time-course of HR in groups S[-], S[g] and S[n]. There were no significant differences in the time-course among the three groups. Panel-C shows the time-course of HR in groups P[-], P[g] and P[n]. There were no significant differences in the time-course among the three groups.

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Figure 4

The time-course of blood lactate levels. Panel-A shows the time-course of lactate levels in groups S[-] and P[-]. *: There were significant differences in the time-course between the two groups, $P < 0.05$, two-way repeated measures ANOVA. #: $P < 0.05$ versus group S[-] at each time-point, Welch test. Panel-B shows the time-course of lactate levels in groups S[-], S[g] and S[n]. There were no significant differences in the time-course among the three groups. Panel-C shows the time-course of lactate levels in groups P[-], P[g] and P[n]. There were no significant differences in the time-course among the three groups.

Figure 5

The time-course of blood glucose levels. Panel-A shows the time-course of glucose levels in groups S[-] and P[-]. *: There were significant differences in the time-course between the two groups, $P < 0.05$, two-way repeated measures ANOVA. #: $P < 0.05$ versus group S[-] at each time-point, Welch test. Panel-B shows the time-course of glucose levels in groups S[-], S[g] and S[n]. †: There were significant differences in the time-course among the three groups, $P < 0.05$, two-way repeated measures ANOVA. ‡: Adjusted $P < 0.05$ versus group S[-] at each time-point, Scheffé F test. Panel-C shows the time-course of glucose levels in groups P[-], P[g] and P[n]. §: There were significant differences in the time-course among the three groups, $P < 0.05$, two-way repeated measures ANOVA. ¶: Adjusted $P < 0.05$ versus group P[-] at each time-point, Scheffé F test.

Figure 6

The time-course of plasma insulin levels. The vertical axis is expressed in a logarithmic scale. Panel-A shows the time-course of insulin levels in groups S[-] and P[-]. *: There were significant differences in the time-course between the two groups, $P < 0.05$, two-way repeated measures

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ANOVA. #: $P < 0.05$ versus group S[-] at each time-point, Welch test. Panel-B shows the time-course of insulin levels in groups S[-], S[g] and S[n]. †: There were significant differences in the time-course among the three groups, $P < 0.05$, two-way repeated measures ANOVA. ‡: Adjusted $P < 0.05$ versus group S[-] at each time-point, Scheffé F test. Panel-C shows the time-course of insulin levels in groups P[-], P[g] and P[n]. §: There were significant differences in the time-course among the three groups, $P < 0.05$, two-way repeated measures ANOVA. ¶: Adjusted $P < 0.05$ versus group P[-] at each time-point, Scheffé F test.

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