EXPERIMENTAL STUDY

Early impairment of insulin secretion in rats after surgical trauma

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Abstract

Objective: Hyperglycaemia associated with insulin resistance is common after trauma and surgical procedures. Both reduced tissue insulin sensitivity and alterations in insulin release may contribute to the impaired glucose homeostasis. We have demonstrated that skeletal muscle insulin resistance is present 2 h after small intestinal resection in rats. In this study, the aim was to investigate insulin secretion in the same experimental model.

Design: Small intestinal resection (5 cm) was performed in adult rats. The control animals underwent anaesthesia only.

Methods: The intravenous glucose tolerance test (IVGTT), the hyperglycaemic clamp and in vitro studies in isolated pancreatic islets were performed after surgery. Concentrations of blood glucose, plasma insulin, corticosterone and interleukin-6 (IL-6) were determined 0–5 h postoperatively.

Results: The insulin response in the IVGTT was attenuated 2 h after small intestinal resection (P < 0.05) but not 4 h or during the hyperglycaemic clamp (3.5–4.5 h) postoperatively. Insulin secretion in response to glucose in vitro was decreased 2 h after the surgery (P < 0.05), but no change was seen in arginine-stimulated secretion. Plasma levels of corticosterone were increased 3.5–5 h postoperatively (P < 0.001–0.05). Increases in IL-6 were also seen postoperatively.

Conclusion: We demonstrate that glucose-induced, but not arginine-induced, insulin secretion is temporarily impaired after intestinal resection in rats. The later appearance of elevated corticosterone and IL-6 levels, as well as the preservation of the beta-cell inhibition in vitro, argues against the possibility that these two circulating factors are causally responsible for reduced insulin release seen after surgery in this model.

European Journal of Endocrinology 147 825–833

Introduction

Hyperglycaemia associated with insulin resistance is common after trauma and surgical procedures (1). Both reduced tissue insulin sensitivity and alterations in insulin release may contribute to the impaired glucose homeostasis. For example, insulin-mediated glucose disposal is impaired both in humans after injury, surgery, burns and sepsis (2–7) and in laboratory animals with injury or sepsis (8–10). Studies investigating insulin concentrations after trauma or surgery have shown inconsistent results. Circulating insulin levels were increased in rodents after burn and traumatic injury (11, 12). In contrast, insulin levels were decreased in baboons after haemorrhagic hypotension (13) and in rats after burn injury (14). In man, insulin levels declined at the start of surgery (15, 16), and the insulin response to glucose was found to be suppressed intraoperatively (17) and soon after surgery (18).

In our model of small intestinal resection in rats, we have investigated the early effects of moderate abdominal surgical trauma on glucose metabolism. In previous studies, we have demonstrated reduced insulin-mediated glucose transport in vitro in skeletal muscle 2 h after intestinal resection (19–21).

Our primary aim in the current study was to investigate glucose-stimulated insulin secretion in vivo early (2 and 4 h) after surgery in this experimental model. Corticosterone and the cytokine interleukin-6 (IL-6) were analysed because of their regulating potential in insulin secretion and because they reflect the endocrine stress response to surgery. Based on the results of the in vivo insulin secretion studies, we performed two additional in vitro experiments. Isolated pancreatic
islets were studied postoperatively (2 h) to assess if alterations in insulin secretion were maintained in the absence of circulating factors. Peripheral insulin sensitivity may affect insulin release and, therefore, we also determined skeletal muscle insulin sensitivity in vitro 4 h after surgery.

Materials and methods

Study design

Small intestinal resection (5 cm) was performed in adult rats. The control animals underwent anaesthesia only. The following four different sets of experiments were performed: (A) Insulin secretion 2 and 4 h after surgery in conscious and unrestrained rats, using either intravenous glucose tolerance test (IVGTT) or the hyperglycaemic clamp technique. (B) Concentrations of blood glucose, plasma insulin, corticosterone and IL-6 were determined 0–5 h after surgery at 30-min intervals. (C) Glucose- and arginine-stimulated insulin secretion in pancreatic islets isolated from rats 2 h after surgery. (D) Basal and insulin-stimulated glucose transport in isolated soleus muscles 4 h after surgery.

Animals and anaesthesia

Male Wistar rats (360–390 g; B&K Universal, Stockholm, Sweden) were housed individually with a 12 h light:12 h darkness cycle and had free access to standard rat chow and water. The rats were conditioned at least 1 week prior to the experiments. All procedures were conducted with approval from the local ethics committee. For induction of anaesthesia, intraperitoneal (i.p.) injection of ketamine and xylazine were used at doses of 70 mg/kg and 10 mg/kg respectively. Rats wake up after approximately 60 min with this anaesthetic procedure.

Surgical trauma model

Rats were anaesthetised and an 8 cm incision was made along the midline of the abdomen. A 5 cm small intestinal resection was performed 5 cm distal to the ligament of Treitz. The intestine was sutured with six interrupted sutures (6/0, Prolene), and the abdominal cavity was closed using 4/0 Vicryl sutures. The surgery took about 10 min to perform. The animals were returned to individual cages and had free access to water. The cages were placed under a heating lamp to help maintain body temperature in the immediate postoperative period.

Catheterisation of the jugular vein and aorta

Catheters were implanted at least 7 days prior to the start of the individual experiments. Animals selected for IVGTTs and for the time-course study of blood chemistry had a jugular vein catheter inserted under aseptic surgical conditions. Rats were given a preoperative i.p. dose of cefazolin (Zinazef, 50 mg/kg) at the time of anaesthesia. Briefly, a silicon catheter was placed in the right jugular vein through a small skin incision on the ventral side of the neck and was tunnelled under the skin to the dorsal side of the neck of the rat. In rats scheduled for the hyperglycaemic clamp, both the abdominal aorta and the jugular vein were catheterised. The aortic catheter was tunnelled retroperitoneally through the muscles of the left flank and under the skin to the dorsal side of the neck. The jugular vein and aortic catheters were exteriorised through the incision at the back of the neck. The procedures for fabrication and implantation of the jugular and abdominal aortic catheters have been described previously (22, 23).

IVGTT

Rats were fasted overnight (16 h) before IVGTT. In the traumatised rats (Trauma group), the IVGTT was started 2 (n = 12) or 4 h (n = 8) after surgery. In the non-traumatised rats (Control group), the test was started 2 h and 10 min (n = 6) or 4 h and 10 min (n = 6) after anaesthesia. Thus, the time intervals from anaesthesia to IVGTT were identical between traumatised and control rats. All animals were conscious and unrestrained at the time of the test. After a baseline blood sample (250 μl) was taken, 0.5 g/kg glucose (30% glucose solution diluted to 1 ml with sterile water) was administered in 1 min through the jugular vein catheter. Two minutes later, blood was sampled (10 μl) to measure blood glucose. Subsequently, blood samples (250 μl) were taken at 5, 10, 20, 30 and 60 min to determine blood glucose and plasma insulin. The area under the curve (AUC) for blood glucose and plasma insulin was computed using the trapezoidal rule approach.

Hyperglycaemic clamp

Rats (n = 9) were fasted overnight and kept in their own cages. The jugular vein catheter was connected to 40 cm polyethylene tubing (PE 20). The aortic catheter was used for blood sampling during the experiment. Blood (250 μl) was drawn for glucose and insulin baselines before the commencement of the experiment. A glucose solution (100 mg/ml in 0.9% NaCl) was infused through the venous catheter at a slow rate. A steady blood glucose concentration (11.5–12.5 mmol/l) was achieved after 98±2 min in all rats and was maintained for 60 min. Blood samples (250 μl) were taken at 0, 20, 40 and 60 min after steady state was achieved. In between, a small blood sample (10 μl) was taken at 5–10-min intervals to measure glucose only. The steady state was maintained by adjusting the rate of glucose input. After 60 min in
Insulin secretion after surgical trauma

Insulin secretion from isolated islets

Islets were collected from traumatised (n = 7) and control (n = 8) rats and pre-incubated for 30 min as described above. Fifty islets from each rat were then incubated for 90 min in 35 mm culture dishes with 2 ml of KRB buffer containing either 5.6 mmol/l glucose, 16.7 mmol/l glucose, or 5.5 mmol/l glucose + 15 mmol/l L-arginine. Ten of the 50 islets were transferred to 0.5 ml acid alcohol (0.1 mol/l HCl in 75% alcohol) and homogenised with a Dounce homogeniser. The homogenates were dried and re-suspended in 500 μl RIA buffer for insulin RIA. The remaining islets were used for measurement of insulin mRNA. Total insulin mRNA was prepared from these islets according to the method described by Chomczynski & Sacchi (25). The amount of insulin mRNA in the sample was determined by competitive RT-PCR, using synthesised RNA as internal standard (26). The synthesised RNA shared primer sequences with insulin mRNA but produced a PCR product of a different length. After known amounts of the internal standard were co-amplified with a set amount of sample RNA, the PCR products were separated by agarose gel electrophoresis. The gel was scanned and the band intensities were quantified to calculate the concentration of insulin mRNA. Values for 18S rRNA were also obtained from competitive RT-PCR and used to correct the insulin mRNA values.

Glucose transport in isolated skeletal muscle

Glucose transport was assessed in isolated soleus muscles (27) in fed rats 4 h after induction of anaesthesia (n = 8) or after anaesthesia and intestinal resection (n = 8). Briefly, muscle strips underwent a 15-min recovery period in incubation buffer (Krebs–Henseleit buffer containing 5 mmol/l HEPES, 0.1% RIA-grade BSA, 2 mmol/l pyruvate, and 18 mmol/l mannitol). The strips were then placed for 30 min in incubation buffer to which 0, 100, 200 or 1000 μU/ml insulin had been added. Finally, the muscle strips were incubated for 10 min in Krebs–Henseleit buffer containing 0.1% BSA, 8 mmol/l U-[3H]-O-methylglucose (2.5 μCi/mmole), 12 mmol/l [14C]mannitol (26.3 μCi/mmole) (ICN Biomedicals, Costa Mesa, CA, USA), and insulin (0, 100, 200 or 1000 μU/ml insulin). All incubations were conducted at 35°C with continuous oxygenation (95% O2/5% CO2). The muscles were processed as previously described (27). Glucose transport
activity was calculated as micromoles of $[^3H]3$-O-methylglucose accumulated per millilitre of intracellular water per hour.

**Blood glucose and RIAs**

Blood glucose was determined enzymatically immediately after sampling (Glucose Analyzer YSI 2000 system, Kebo, Stockholm, Sweden). Immunoreactive insulin in plasma was measured by RIA using $^{125}$I-labelled porcine insulin as the tracer and rat insulin as the standard, and antibodies against porcine insulin (28). Plasma corticosterone was analysed using RIA from ICN Biomedicals. IL-6 was analysed by solid phase ELISA from R&D Systems (Minneapolis, MN, USA). In the *in vitro* study, insulin concentration in incubation media was measured using RIA kits for rat insulin (Linco Research, Inc., St Charles, MO, USA).

**Statistical analysis**

Data are presented as means±S.E.M., except for the IL-6 data. The IVGTT data, glucose transport experiments and the glucose, insulin and corticosterone data were analysed by analysis of variance (ANOVA) followed by the Bonferroni post-test for multiple comparisons. The data from the hyperglycaemic clamp experiment were assessed with the Student’s paired $t$-test. The Student’s unpaired $t$-test was used to analyse the data from the isolated islet experiments. The control data from the IL-6 measurements did not pass the normality test due to the low number of values over the detection limit, and therefore statistical analysis between control and trauma levels was not feasible. $P < 0.05$ was considered statistically significant in all analyses.

**Results**

**Intravenous glucose tolerance test 2 h after surgical trauma (Fig. 1)**

Fasting blood glucose values were not significantly different between traumatised and control rats (5.3±0.3 vs 4.7±0.3 mmol/l). In both groups, blood glucose concentrations peaked 2 min after the intravenous glucose load. Blood glucose levels were significantly higher at 20, 30 and 60 min in the traumatised rats compared with control animals ($P < 0.05$, Fig. 1A). The blood glucose AUC (area under the curve) between 0 and 10 min was similar in traumatised and control rats (69±2 vs 63±3 mmol . min). Between 10 and 60 min, the blood glucose AUC was significantly higher in traumatised rats compared with controls (229±13 vs 137±19 mmol . min, $P < 0.05$).

Fasting plasma insulin was not significantly different between traumatised and control rats (11±1 vs 13±2 µU/ml). The acute insulin response, i.e. 5 min after the intravenous glucose load, was significantly decreased in traumatised rats compared with controls (25±3 vs 57±18 µU/ml, $P < 0.05$, Fig. 1B). Likewise, the AUC for plasma insulin between 0 and 10 min was significantly lower in traumatised rats compared with controls (81±17 vs 267±94 µU/ml . min, $P < 0.05$), but the 10–60 min plasma insulin AUC values were not significantly different (287±77 vs 350±101 µU/ml . min) between the groups.

**Intravenous glucose tolerance test 4 h after surgical trauma (Fig. 2)**

Fasting blood glucose values were not significantly different between traumatised and control rats (5.5±0.7 vs 4.1±0.3 mmol/l). In both traumatised and control rats, blood glucose concentrations peaked 2 min after the intravenous glucose load. No significant changes in blood glucose levels were found at any time points between traumatised and control rats.
Fasting insulin levels in traumatised rats were significantly higher compared with controls (23 ± 2 vs 14 ± 2 μU/ml, P < 0.05, Fig. 2B) and compared with insulin levels sampled 2 h after intestinal resection (23 ± 2 vs 11 ± 1 μU/ml, P < 0.05, Figs 2B and 1B respectively). Plasma insulin levels were not significantly different from controls at 5, 10, 20, 30 or 60 min after glucose injection (Fig. 2B). The AUC values between 0–10 min and 10–60 min for blood glucose or plasma insulin were not significantly different between traumatised and control rats.

**Hyperglycaemic clamp (Fig. 3)**

When fasting circulating levels of glucose and insulin obtained before the preoperative hyperglycaemic clamp were compared with values for the postoperative clamp, there were no significant differences for either the glucose levels (5.1 ± 0.3 vs 5.2 ± 0.4 mmol/l) or the insulin concentrations (9 ± 0.3 vs 10 ± 2 μU/ml).

During the 60 min steady state period, the blood glucose concentration was between 11.5 and 12.5 mmol/l (Fig. 3). When the preoperative and postoperative clamps were compared, no significant differences were seen in the plasma insulin levels at the initial point or at 20, 40 or 60 min of the steady state. Arginine injection resulted in a significant increase in plasma insulin after 2 min compared with the preceding level, but there were no differences in the insulin response to arginine in the preoperative and postoperative clamps. In keeping with the arginine-induced insulin release, blood glucose was significantly reduced 6 min after arginine injection, but the hypoglycaemic effect of arginine was not different between the pre- and postoperative clamps. The glucose infusion rates during the pre- and postoperative clamps were similar (17.0 mg/kg per min vs 17.9 mg/kg per min).

**Blood chemistry (Figs 4 and 5)**

Blood glucose levels was significantly increased at 3.5, 4.0, 4.5 and 5 h in fed rats compared with fed controls (P < 0.001–0.05, Fig. 4A). The plasma insulin concentration showed a significant early decrease at 0.5 h in both groups, but was then similar in fed traumatised and fed control rats throughout the observation period (P < 0.01, Fig. 4B). One hour after anaesthesia or surgery, corticosterone levels were decreased compared with the preoperative level (P < 0.01). No significant differences between groups of animals were seen in the first 3 h. At 3.5, 4.0, 4.5 and 5 h, corticosterone levels were higher in traumatised animals compared with anaesthesia alone (P < 0.05 and
Preoperative levels of IL-6 were below the detection limit (<31.2 pg/ml), as is normal in the rat under basal conditions. In fed traumatised animals, IL-6 was increased in the majority of the animals between 1.5 and 3 h, and in all animals between 3.5 and 5 h after intestinal resection (Fig. 5B). In contrast, in the fed control rats, increased levels of IL-6 were found in only a few animals per investigated time-point between 0.5 and 5 h after anaesthesia (Fig. 5B).

**Insulin secretion from isolated islets (Fig. 6)**

Basal (5.6 mmol/l glucose) insulin secretion in islets isolated 2 h after surgery or anaesthesia was not significantly different between traumatised and control animals. However, insulin secretion induced by 16.7 mmol/l glucose was significantly decreased in islets isolated from traumatised rats compared with those from control animals (18.4±8.6 vs 35.1±13.9 ng/5 islets, P < 0.01). No significant differences were found for arginine-stimulated insulin secretion between islets from traumatised and control rats.
Islet insulin content and mRNA expression

No significant differences were found in insulin content (ng insulin/five islets) between islets from traumatised and control rats under basal conditions (715±159 vs 707±254), glucose stimulation (777±249 vs 815±96), or arginine stimulation (704±319 vs 732±87). Similarly, insulin mRNA (ng/μg total RNA) expression was not statistically different between control and traumatised rats under basal conditions (8.0±1.3 vs 9.9±1.0), glucose stimulation (8.7±0.5 vs 8.7±2.5), or arginine stimulation (11.7±2.6 vs 14.0±1.4).

Glucose transport in isolated skeletal muscle (data not shown)

Basal (no insulin) glucose transport was 1.7±0.4 in control and 1.3±0.2 μmol/ml per hour in traumatised rats. The response to sub-maximal (100 and 200 μU/ml) and maximal (1000 μU/ml) insulin stimulation was similar in traumatised and control rats (2.5±0.4 vs 2.1±0.4, 2.8±0.1 vs 2.6±0.3 and 5.8±0.7 vs 4.6±0.4 μmol/ml per hour respectively) and no significant differences were seen between the groups.

Discussion

In the current study, small intestinal resection in rats resulted in a short-term impairment of glucose-induced, but not arginine-induced, insulin secretion and skeletal muscle insulin sensitivity 2 h after surgery. These trauma-induced alterations were not associated with an increase in circulating corticosterone or IL-6.

Surgical trauma had no effect on fasting glucose and insulin levels, apart from a small increase in plasma insulin in traumatised rats 4 h (before the IVGTT, Fig. 2) after intestinal resection. However, this increase in fasting plasma insulin could be due to the slightly elevated fasting blood glucose level at this time point, indicating a normal beta-cell response. In the time-course studies in fed rats, blood glucose was higher 3.5–5 h postoperatively, showing that small intestinal resection is sufficient to induce hyperglycaemia. The early defect in glucose-induced insulin secretion in traumatised rats at 2 h after surgery could have contributed to the later appearing (3.5–5 h) trauma-induced hyperglycaemia. An early temporary reduction in plasma insulin (0.5 h) was seen in both groups of rats. Suppression of plasma insulin early after induction of anaesthesia has been observed previously in surgical patients (15, 16) and has been suggested to be due to anaesthesia alone and not related to the surgical trauma (29).

When the traumatised rats were challenged with a glucose bolus 2 h after surgical trauma, their first phase insulin secretion (5 min) was shown to be impaired. This finding is in line with previous observations of suppressed insulin responses to a glucose or tolbutamide injection within 2 h after trauma in animal models (13, 30) and in man during and shortly after surgery (17, 18, 31). However, when the beta-cell response to a glucose bolus was investigated 4 h after intestinal resection, the insulin response was similar in traumatised and control rats. Similarly, during the postoperative hyperglycaemic clamp, insulin levels determined 3.5–4.5 h after surgery were not different from the results found in the preoperative hyperglycaemic clamp. The hyperglycaemic clamp method offers a highly physiological technique of quantifying beta-cell sensitivity to glucose in vivo (32). In addition, the glucose infusion rate during the clamp gives an estimate of whole-body glucose uptake. In our experiments, the glucose infusion rates in the pre- and postoperative clamps were not different, which suggests unaltered glucose uptake at 3.5–4.5 h after surgery. In support of this, insulin-stimulated glucose transport in isolated skeletal muscles was unaltered 4 h after intestinal resection. Taken together with our previous repeated findings of reduced insulin-stimulated glucose transport 2 h after surgery (19–21), the results of the present study show that the trauma-induced impairments in both glucose-stimulated insulin secretion and insulin sensitivity are present 2 h after surgery, but not 4 h after surgery. Therefore, the significant increase in blood glucose levels found 4 h after surgery (Fig. 4A) is more likely due to an increase in endogenous glucose production rather than a reduction in insulin-mediated glucose uptake.

It is possible that the reduced glucose-stimulated insulin secretion after 2 h in vivo is mediated by increased levels of circulating insulin-antagonistic hormones, such as adrenaline and corticosterone. Both these hormones have been shown to inhibit insulin secretion in vivo (33, 34) and in vitro (35–37). Also, the cytokine IL-6 has been shown to inhibit glucose-stimulated insulin secretion from isolated rat pancreatic islets (38–40). Plasma levels of adrenaline are elevated in our trauma model 2 h postoperatively (19, 21) and represent a potential circulating factor that could impair insulin secretion early after surgery. In the current study, we evaluated the impact of increased plasma corticosterone and IL-6 on insulin release after surgery. When insulin secretion was impaired in traumatised rats (2 h), plasma levels of corticosterone and IL-6 were not significantly increased in these animals compared with controls (Fig. 5). In contrast, when plasma corticosterone and IL-6 levels subsequently increased 3.5–5 h after trauma, insulin secretion was normalised. This suggests that increased circulating levels of corticosterone and IL-6 do not have any major impact on insulin release after intestinal resection in the rat.

A marked decrease in plasma corticosterone was observed in both groups of rats 1 h after induction anaesthesia or anaesthesia and surgery (Fig. 5A). Similar
to plasma insulin levels as discussed above, this pattern has previously been observed in man early after induction of anaesthesia (16, 41). Our present observation indicates that this effect of anaesthesia may also be present in rodents. In man, the increase in IL-6 is related to the magnitude of the surgery (42) and can be used as a marker of surgical stress. This cytokine has been reported to increase five- to sixfold after upper abdominal surgery in man (43). In our study, IL-6 was increased approximately sevenfold, which suggests that our experimental model is comparable to moderate surgery in man. The parallel postoperative increase in corticosterone also shows that the trauma-induced endocrine response is initiated at 3 h after surgery in this model. Therefore, the impairment of insulin secretion and skeletal muscle insulin sensitivity after intestinal resection in the rat does not seem to occur in parallel with the endocrine response. This finding is line with previous studies in man suggesting that circulating concentrations of stress hormones may be of less importance for early insulin resistance after surgical trauma (6).

To examine whether the inhibition of glucose-stimulated insulin release observed in vivo at 2 h after surgery was mediated by extra-pancreatic factors, we performed additional in vitro experiments. An adverse effect of surgical trauma on the insulin response to glucose was seen in pancreatic islets isolated 2 h after intestinal resection. Thus, the trauma-induced effects upon the beta cells seen in vivo were maintained in vitro in the absence of circulating factors. However, in another in vitro system, the isolated perfused rat pancreas, catecholamines are present in high concentrations within the gland even after isolation (44). Presence of catecholamines within isolated islets from traumatised rats may be one mechanism that could explain the maintenance of inhibition of insulin release in vitro.

The effect of arginine on insulin release was also studied in vitro to investigate whether the pancreatic beta cell was responsive to a non-glucose, non-metabolised secretagogue when the insulin response to glucose was impaired. No differences in the insulin response to arginine were seen in vitro between the islets from traumatised and control rats, indicating that trauma-induced effects on the beta cell may be confined to glucose. This could be due to differential beta-cell sensitivity to various secretagogues in the acute phase after surgical trauma, either by interference in metabolism of glucose and the subsequent events leading to beta-cell depolarisation, or by alteration of the direct effect of glucose on insulin exocytosis (45). In vivo, insulin levels after arginine injection were similar in the pre- and postoperative hyperglycaemic clamp. The unaltered response is not surprising since no impairment of insulin release was demonstrated at this time point.

We also determined the insulin content and mRNA expression in the isolated pancreatic islets and found no significant differences between traumatised and control rats. This suggests that the process of secretion, but not of production, is affected by surgery.

In conclusion, we found that glucose-induced, but not arginine-induced, insulin secretion is temporarily impaired after intestinal resection in rats. The later appearance of elevated levels of corticosterone and IL-6, as well as the preservation of the beta-cell inhibition in vitro, argue against the possibility that these two circulating factors are causally responsible for the reduced insulin release seen in this model.

Acknowledgements

This study was supported by grants from the Swedish Medical Research Council (nos 00034 and K99-72X-1265-02B) and the Swedish Diabetes Association. We would like to thank Beth Arnbjørn, Susanne Bergstedt-Lindqvist, Irén Engström, Elvi Sandberg and Annika Wagman for skilful assistance, and Ronald Prigeon, University of Washington, Seattle, for helpful comments.

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