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Preoperative glucocorticoid administration attenuates the systemic stress response and hyperglycemia after surgical trauma in the rat

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Abstract

The stress response to surgery is characterized by activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, and by an inflammatory response and hyperglycemia. The aim of the present study was to investigate if preoperative corticosterone could reduce the postoperative systemic stress response, without aggravating hyperglycemia or interfering with activation of the hypothalamic-pituitary-adrenal axis, in a standardized rat model of surgical trauma. We used a standardized experimental model of intestinal resection in the rat. Exogenous corticosterone (8 mg/kg body weight) or vehicle was administered 2 hours before surgery; and postoperative plasma concentrations of interleukin-6, interleukin-10, adrenaline, noradrenaline, glucose, and insulin were determined. Exogenous corticosterone decreased preoperative plasma adrenaline but did not change plasma glucose or insulin levels. Moreover, corticosterone reduced postoperative plasma interleukin-6, catecholamines, and glucose (all $P < .001$-.05) without any effect on the plasma corticosterone concentration compared with vehicle-treated controls. A preoperative 2-hour exposure of physiologic poststress corticosterone concentrations not only suppressed plasma IL-6 levels but also inhibited surgery-induced adrenaline release and suppressed plasma glucose levels. We hypothesize that glucocorticoids attenuated the inflammatory response in injured tissues that reduced afferent input into brain areas regulating the neuroendocrine response.

1. Introduction

The stress response after surgery includes the activation of the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic-nervous system (SNS), and the immune system and is essential for maintaining homeostasis within the host. This adaptive response results in increased circulating levels of stress hormones (glucocorticoids, catecholamines, glucagon) and in metabolic changes toward catabolism characterized by hyperglycemia [1-4].

Glucocorticoids are of particular interest in the systemic stress response because of their complex actions. On one hand, glucocorticoids are able to suppress the inflammatory response [5] and thereby hyperglycemia [4,6]; but on the other hand, glucocorticoid excess could result in a diabetes-like state [7,8]. Furthermore, high levels of glucocorticoid constitute an early protective response to stress; and attenuated endogenous glucocorticoid secretion could be detrimental in a situation of hypovolemia [9]. Hyperglycemia, high levels of glucocorticoid, and reduced responsiveness of the HPA axis occur after surgery in human patients [10]. These changes are also found in our rat model of surgical trauma designed for postoperative metabolic studies [11-15].

The aim of the present study was to investigate if preoperative corticosterone (Cort) (the active glucocorticoid in rats) could reduce the postoperative stress response,

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without aggravating hyperglycemia or interfering with activation of the HPA axis, in a standardized rat model of surgical trauma. The dose-response effects and kinetic studies of subcutaneously administered Cort on plasma Cort and glucose were determined. We studied the effects of Cort on the inflammatory response, sympathetic-adrenal system, and glucose metabolism by measuring concentrations of Cort, plasma interleukin (IL)-6, IL-10, noradrenaline, adrenaline, glucose, and insulin.

2. Material and methods

2.1. Animals

Male Wistar rats (330-360 g; B & K Universal, Stockholm, Sweden) were housed individually with a 12-hour light/dark cycle with the light cycle starting at 6:00 AM. Rats had free access to standard rat chow and water. Animals were conditioned by daily handling and weighing for at least 1 week before the insertion of the jugular catheters. All procedures were conducted with approval from the local ethics committee.

2.2. Catheterization of the jugular vein

Rats were given a preoperative intraperitoneal dose of cefazolin (50 mg/kg) at the time of anesthesia as prophylaxis against infection. A silicon catheter was placed in the right jugular vein through a small skin incision on the ventral side of the neck and was tunneled under the skin to the dorsal side of the neck of the rat. The process of fabrication and implantation of the jugular catheters has been described previously [16]. Rats were allowed to recover for a minimum of 1 week after the surgical catheterization procedure before the experiments were started. During the recovery period, the animals were handled and weighed daily and accustomed to blood sampling procedures by flushing the catheter. Rats that failed to gain weight during the recovery period were excluded from the experiments.

2.3. Administration of Cort

All experiments started between 6:00 and 8:00 AM to minimize circadian interference. Animals in the vehicle (Veh) groups received 200 μL propylene glycol subcutaneously. Corticosterone (C2505; Sigma Aldrich, St Luis, MO) was dissolved in 200 μL propylene glycol and injected subcutaneously at 8 mg/kg.

2.4. Study design

Two hours after the injection of Cort or Veh, the rats were subdivided randomly into anesthesia-only groups (Cort-Control and Veh-Control) and surgery groups (Cort-Trauma and Veh-Trauma) (n = 8 for each of the 4 groups). Plasma Cort, glucose, and insulin were investigated for 4 hours, with the administration of anesthesia occurring 2 hours after the injection of Cort or Veh. A similar experimental protocol was used with 32 other rats for the study of plasma IL-6 and IL-10, and with 32 more rats for measurement of adrenaline and noradrenaline. In an additional set of 32 rats, plasma Cort and glucose were investigated during the period from 6 to 30 hours after anesthesia/surgery or anesthesia alone.

2.5. Anesthesia

Rats were premedicated with 1 mg/kg midazolam subcutaneously 15 minutes before anesthesia was induced. For induction, rats were put in airtight anesthetizing chambers containing 4% isoflurane. The animals were then removed from the chambers and breathed 1.5% to 3% isoflurane through a nose cone connected to a vaporizer (Univentor 400; Agntho's, Lidingö, Sweden) for 15 minutes in both the control and trauma groups. Buprenorphine hydrochloride (0.075-0.01 mg/kg body weight) was given subcutaneously after the induction of anesthesia for postoperative pain relief. The depth of anesthesia was controlled during all procedures. The rats were placed on heating pads during anesthesia to maintain body temperature.

2.6. Blood sampling procedures

No sedation or anesthesia was used during blood sampling from the jugular catheters. The sampled blood was replaced with twice the volume of intravenous saline (0.9% NaCl) to avoid hypovolemia. Blood samples (450 μL) for basal levels were drawn between 6:00 and 8:00 AM 3 days before the injection of Cort or Veh. Thereafter, blood samples (450 μL each) were taken at −1.5 hours, −5 minutes, +15 minutes, +45 minutes, and +2 hours in the 4-hour experiments. The *zero time point* was defined as the moment when rats were removed from the anesthetizing chamber. In the 32-hour experiment, 450-μL blood samples were taken at +6, +18, +26, and +30 hours. Blood was collected in chilled tubes containing 10 μL EDTA (0.250 mol/L, pH 8.0) and kept on ice. After the tubes were centrifuged at 4°C for 15 minutes at 3000 rpm, the plasma was removed and stored at −70°C until analysis.

2.7. Determination of the dosage of Cort

Briefly, rats had received indwelling jugular catheters as described above and were divided into 3 groups. The animals received Cort (8 mg/kg, n = 10 or 16 mg/kg, n = 10) or Veh (n = 10) subcutaneously. Blood samples (250 μL) for basal levels were drawn between 6:00 and 8:00 AM 3 days before the injection of Cort or Veh. Thereafter, blood samples (250 μL) for determination of plasma Cort and glucose were drawn at 2, 4, 8, 24, 28, and 32 hours after injection. The sampled blood was replaced with twice the volume of intravenous saline (0.9% NaCl) to avoid hypovolemia (Fig. 1A and B).

2.8. Surgery

In the groups receiving surgery, a 5-cm incision was made along the midline of the abdomen. A 5-cm–long resection of

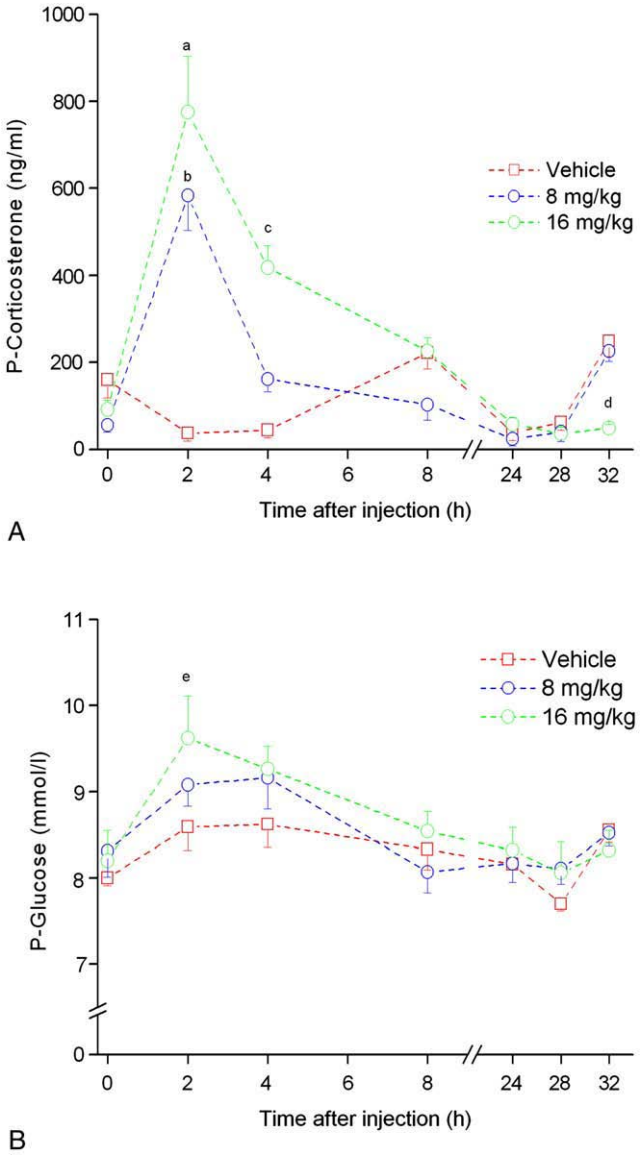

Fig. 1. Plasma Cort (A) and glucose (B) in rats after a subcutaneous injection of Veh (n = 10), 8 mg Cort per kilogram (n = 10), or 16 mg Cort per kilogram (n = 10). A, [a]$P < .001$ 16 mg/kg vs Veh; [b]$P < .001$ 8 mg/kg vs Veh; [c]$P < .001$, [d]$P < .05$ 16 mg/kg vs 8 mg/kg and Veh. B, [e]$P < .05$ 16 mg/kg vs Veh.

the small intestine was performed 5 cm distal to the ligament of Treitz. The intestine was sutured with 6 interrupted nonabsorbable sutures (6/0, Prolene, Ethicon, Somerville, NJ), and the abdominal cavity was closed using interrupted absorbable sutures (4/0 Vicryl, Ethicon). The surgical procedure lasted about 15 minutes. After surgery, animals were returned to individual cages and had free access to water and food.

2.9. Laboratory analysis

Plasma Cort was analyzed using a radioimmunoassay kit from ICN Biomedicals (Costa Mesa, CA). Plasma glucose was determined enzymatically (Glucose Analyzer YSI 2000 system; Kebo, Stockholm, Sweden). Immunoreactive insulin in plasma was measured by radioimmunoassay using ^{125}I-labeled porcine insulin as the tracer, rat insulin as the standard, and antibodies against porcine insulin. Interleukin-6 and IL-10 analysis was performed using the quantitative sandwich enzyme immunoassay technique (R & D Systems, Minneapolis, MN). Plasma noradrenaline and adrenaline concentrations were determined by high-performance liquid chromatography with electrochemical detection. For extraction, 120-μL aliquots of the plasma sample, 0.22 ng of the internal standard 3,4-dihydroxybenzylamine, and 1.5 mol/L Tris buffer (pH 8.6, containing 10 nmol/L EDTA-2Na) were applied to the cartridges, which were then washed with 120 μL of 2% acetic acid containing 100 μmol/L EDTA-2Na. The collected samples were transferred onto a TopTip C18 pipette tip cartridge (ZirChrom, Anoka, MN), and 20 μL of each eluate was injected onto the high-performance liquid chromatography column. The mobile phase was a mixture of methanol and 0.1 mol/L phosphate buffer (pH 5.7) (89:11, vol/vol) containing 2.8 mmol/L octanesulfonic acid sodium salt and 0.13 mmol/L EDTA-2Na [17,18]. The chromatograms were recorded and integrated by use of the computerized data acquisition system Clarity (Data Apex, Prague, Czech Republic).

2.10. Statistical analysis

Data are presented as mean ± SEM. Plasma concentrations data were analyzed by 2-way analysis of variance, with the Bonferroni correction for multiple comparisons. P less than .05 was considered to be statistically significant.

3. Results

3.1. Plasma Cort

Basal levels of plasma corticosterone were similar between the groups. The administration of 8 mg/kg Cort resulted in increased plasma Cort levels at −1.5 hours, −1 hour, and −5 minutes in comparison with rats given Veh (all $P < .001$). At the +15-minute time point, plasma Cort was higher in the Cort-Control compared with Veh-Control group ($P < .01$) and higher in the Cort-Trauma compared with Veh-Trauma group ($P < .01$), but there was no difference between the 2 trauma groups at all other postoperative time points. Plasma Cort levels were higher in the Cort-Trauma compared with Cort-Control group at +15 and +45 minutes (both $P < .05$); at +45 minutes ($P < .01$); and at +1, +2, and +6 hours (all $P < .001$). In the Veh-Trauma group, plasma Cort levels were increased compared with the Veh-Control group at +15 minutes ($P < .01$) and at +1 ($P < .01$), +2, and +6 hours (both $P < .001$) (Fig. 2).

3.2. Plasma IL-6 and IL-10

At the −2-hour, −1.5-hour, and −5-minute time points, plasma IL-6 levels were not different between rats given Veh and those given Cort. At +45 minutes, plasma IL-6 levels were higher in the Veh-Trauma group compared with the

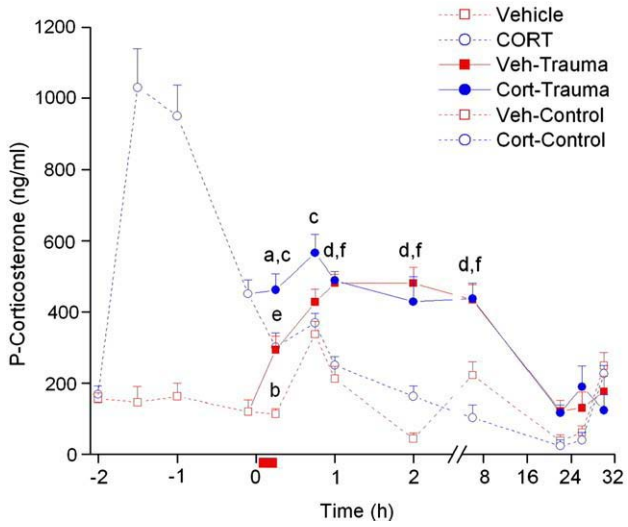

Fig. 2. Plasma Cort in rats before and after a subcutaneous injection of Veh (n = 16) or 8 mg Cort per kilogram (n = 16). Two hours after Veh or Cort administration, the rats within each group were subjected to anesthesia (Veh-Control and Cort-Control) or anesthesia and surgical trauma (Veh-Trauma and Cort-Trauma). The red rectangle indicates the time when animals were subjected to anesthesia. [a]$P < .01$ Cort-Trauma vs Veh-Trauma; [b]$P < .01$ Veh-Control vs Cort-Control; [c]$P < .05$, [d]$P < .001$ Cort-Trauma vs Cort-Control; [e]$P < .01$, [f]$P < .001$ Veh-Trauma vs Veh-Control.

Veh-Control group ($P < .01$), the Cort-Trauma group ($P < .05$), and the Cort-Control group ($P < .001$). At +2 hours, IL-6 levels were higher in the Veh-Trauma group compared with the Veh-Control group, the Cort-Trauma group, and the Cort-Control group (all $P < .001$). At +2 hours, IL-6 levels in the Cort-Trauma group were increased compared with the Cort-Control and Veh-Control groups (both $P < .001$). Plasma IL-10 levels were not different between the groups at any time point (Fig. 3A and B).

3.3. Plasma adrenaline and noradrenaline

Basal levels of plasma catecholamines were not different in the Veh- and Cort-treated groups. Plasma adrenaline was lower in the Cort compared with Veh group at −1.5 hours ($P < .01$). At +45 minutes, plasma adrenaline levels were higher in the Veh-Trauma group compared with the Veh-Control group ($P < .05$), the Cort-Trauma group ($P < .01$), and the Cort-Control group ($P < .001$). At +2 hours, adrenaline levels were increased in the Veh-Trauma group compared with the Veh-Control, Cort-Trauma, and Cort-Control groups (all $P < .001$). At the −1.5-hour and −5-minute time points, plasma noradrenaline levels were not different between rats given Veh and animals given Cort. At +45 minutes, plasma noradrenaline levels were higher in the Veh-Trauma group than in the Cort-Trauma group ($P < .05$) (Fig. 4A and B).

3.4. Plasma glucose and insulin

Plasma glucose and insulin levels were similar in the Veh- and Cort-treated groups before anesthesia. At +15 minutes, plasma glucose levels were higher in all groups compared with the respective glucose concentrations 5 minutes before anesthesia (all $P < .001$). In the Veh-Trauma group, plasma glucose levels were higher at +15 minutes compared with the Veh-Control rats and the Cort-Trauma group (both $P < .001$). Plasma insulin levels were not different between rats given Veh and those given Cort at the −1.5-hour and −5-minute time points. At +15 minutes, plasma insulin levels were increased in the Veh-Trauma group compared with the Veh-Control, Cort-Trauma, and Cort-Control groups (all $P < .001$) (Fig. 5A and B).

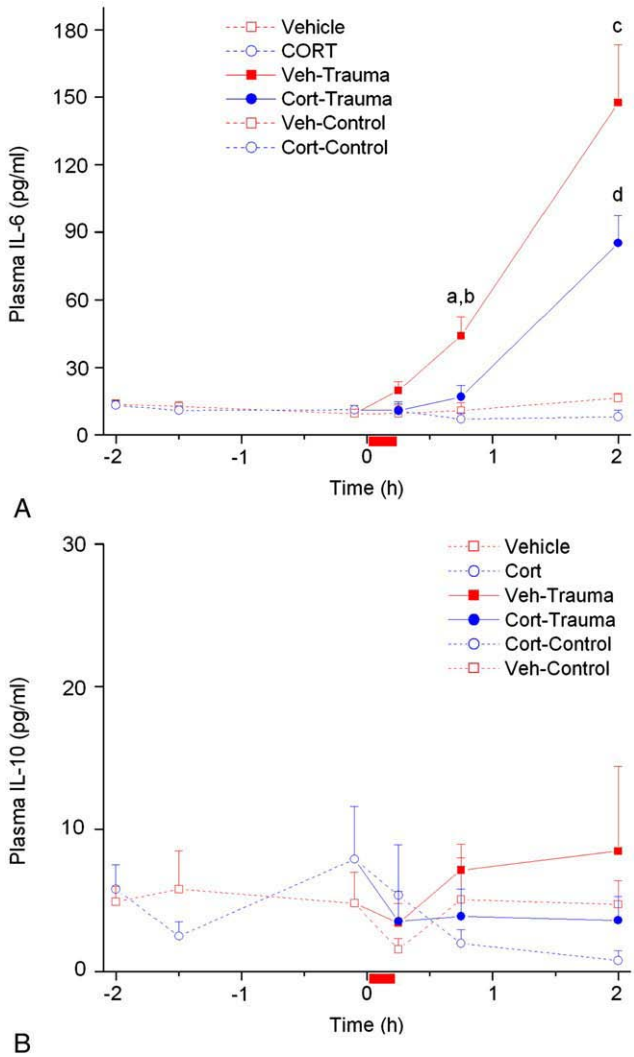

Fig. 3. Plasma IL-6 (A) and IL-10 (B) in rats before and after a subcutaneous injection of Veh (Veh, n = 16) or 8 mg Cort per kilogram (Cort, n = 16). Two hours after Veh (Veh) or Cort (Cort) administration, the rats within each group were subjected to anesthesia (Veh-Control and Cort-Control) or anesthesia and surgical trauma (Veh-Trauma and Cort-trauma). The red rectangle indicates the time when animals were subjected to anesthesia. A, [a]$P < .01$ Veh-Trauma vs Veh-Control; [b]$P < .05$ Veh-Trauma vs Cort-Trauma; [c]$P < .001$ Veh-Trauma vs Cort-Trauma and Veh-Control; [d]$P < .001$ Cort-Trauma vs Cort-Control and Veh-Control.

4. Discussion

There were 2 main findings of the present study. Firstly, a preoperative single dose of Cort attenuated the postoperative systemic increase in plasma IL-6 and inhibited the adrenaline response. Secondly, these effects were achieved without aggravated postoperative hyperglycemia or attenuated Cort levels.

The dose of 8 mg/kg of Cort resulted in physiologic poststress levels of plasma Cort that did not cause hyperglycemia or impair the circadian rhythm. Previous studies investigating the effect of glucocorticoids on the stress response after various types of stressors [19,20] showed a maximal inhibition of the stress response when the stressor occurred at the time of high levels of circulating glucocorticoids [19]. As shown in Fig. 1, plasma Cort levels were maximal 2 hours after Cort (8 mg/kg) administration. Therefore, this time point was chosen for the start of the surgical procedure in the subsequent experiments. Our subsequent experiments indicated that the 8-mg/kg dose did not attenuate surgery-induced endogenous hypercorticosteronemia.

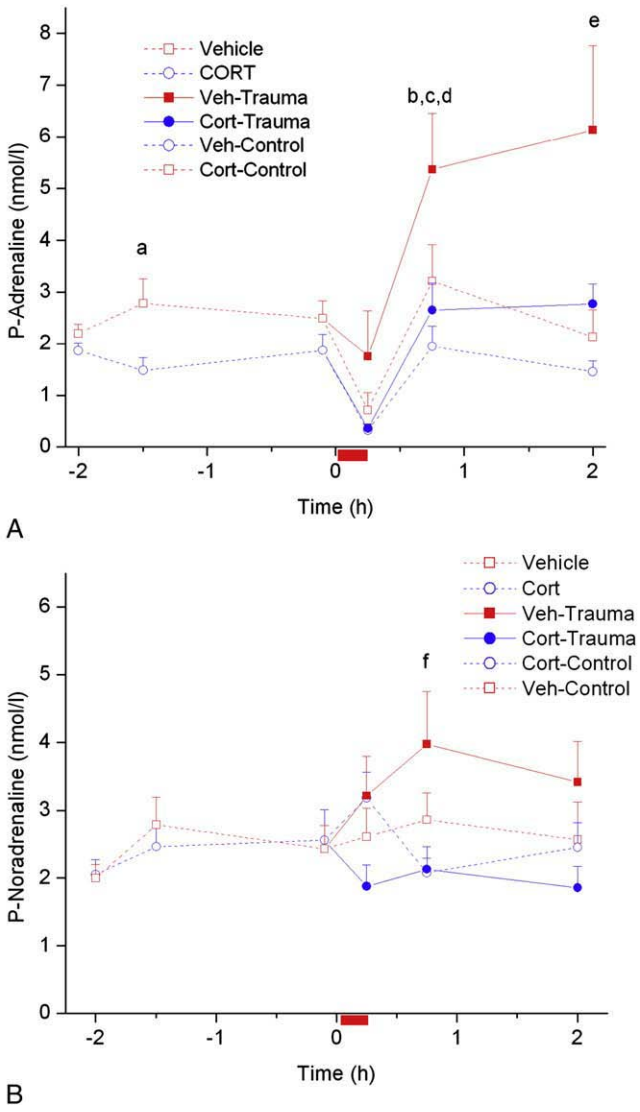

Fig. 4. Plasma adrenaline (A) and noradrenaline (B) in rats before and after a subcutaneous injection of Veh (n = 16) or 8 mg Cort per kilogram (n = 16). Two hours after Veh or Cort administration, the rats within each group were subjected to anesthesia (Veh-Control and Cort-Control) or anesthesia and surgical trauma (Veh-Trauma and Cort-Trauma). The red rectangle indicates the time when animals were subjected to anesthesia. A, $^{a}P < .01$ Veh vs Cort; $^{b}P < .05$ Veh-Trauma vs Veh-Control; $^{c}P < .01$ Veh-Trauma vs Cort-Trauma; $^{d}P < .001$ Veh-Trauma vs Cort-Control; $^{e}P < .001$ Veh-Trauma vs all other groups. B, $^{f}P < .05$ Veh-Trauma vs Cort-Trauma and Cort-Control.

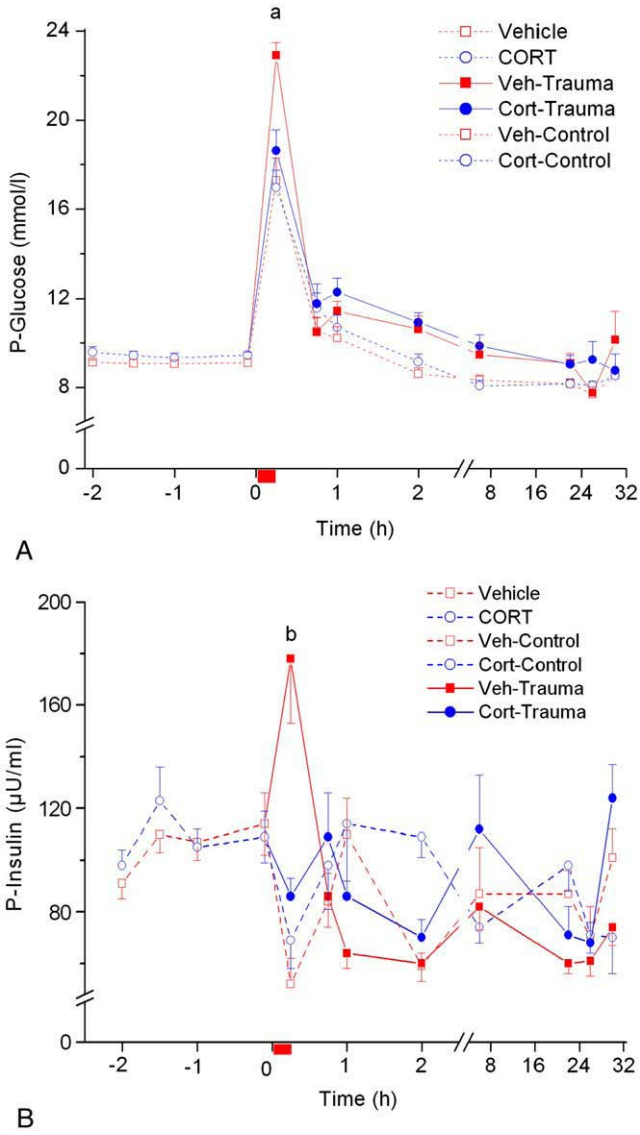

Fig. 5. Plasma glucose (A) and insulin (B) in rats before and after a subcutaneous injection of Veh (n = 16) or 8 mg Cort per kilogram (n = 16). Two hours after Veh or Cort administration (time zero), the rats within each group were subjected to anesthesia (Veh-Control and Cort-Control) or anesthesia and surgical trauma (Veh-Trauma and Cort-trauma). The red rectangle indicates the time when animals were subjected to anesthesia. A, $^{a}P < .001$ Veh-Trauma vs Veh-Control, Cort-Trauma. B, $^{b}P < .001$ Veh-Trauma vs Veh-Control, Cort-Trauma, Cort-Control.

The proinflammatory cytokine IL-6 is one of the primary mediators of the acute stress response to injury [21] and stimulates stress hormone release in man [22-25]. In the present study, the postoperative reduction of circulating IL-6 levels could be caused by an inhibitory effect of Cort on surgery-induced inflammation and subsequent cytokine release. Interestingly, these marked effects were observed after such a short preoperative exposure (2 hours) to physiologic concentrations of the hormone. However, similar rapid responses on inflammation (eosinophil inflammation and leukotriene-B4 levels) have been observed in mice given glucocorticoids corresponding to physiologic levels 2 hours before asthma induction [26]. In patients given a single preoperative dose of methylprednisone (10 mg/kg) 30 minutes before esophageal surgery, plasma IL-6 and IL-10 concentrations were reduced and increased, respectively [20]. In vitro, glucocorticoids are known to counteract lipopolysaccharide-stimulated IL-6 production and release from human monocytes and endothelial cells [27]. Taken together, we hypothesize that glucocorticoids act anti-inflammatorily on lymphoid tissue, which results in an attenuated proinflammatory cytokine release in response to a surgical stimulus.

Preoperative Cort administration reduced plasma adrenaline levels after surgery to levels similar to control animals. Thus, surgery-induced adrenaline release was inhibited by Cort. The reduction in noradrenaline was not as pronounced as the changes in plasma adrenaline. Noradrenaline is secreted locally from sympathetic nerve endings, and local changes in noradrenaline release are not necessarily reflected in the systemic concentration [28]. The immune system is tightly connected with the SNS and the HPA axis to adapt the host to acute challenges by ensuring energy substrate mobilization, cardiovascular and hemodynamic compensation, as well as immune function and tissue repair. This connection is called the *inflammatory reflex* [2] and involves afferent and efferent nerve fibers from lymphoid tissue to and from the central nervous system, in particular the paraventricular nucleus of the hypothalamus and the locus coeruleus [1]. According to this, Cort could have reduced cytokine release in lymphoid tissues, which in turn attenuated the afferent input from injured tissues into brain regions important for sympathetic output, directly via afferent neurons and indirectly via reduced release of cytokines into the circulation. This mechanism would result in an attenuated activation of the SNS with a subsequent reduction in catecholamine release.

It is also possible that high preoperative Cort concentrations early after injection, via negative feedback on corticotropin release [29], caused a sustained inhibition of the adrenal medullary enzyme phenylethanolamine-*N*-methyltransferase. Phenylethanolamine-*N*-methyltransferase is induced by very high local concentrations of glucocorticoid delivered by the adrenal's portal vascular system and favors the conversion of noradrenaline to adrenaline [30]. Thus, reduced corticotropin stimulus of the adrenal cortex causing lower local glucocorticoid concentrations in the adrenal medulla could be another mechanism that contributed to reduce plasma adrenaline release into the circulation with or without surgical stimulus. Although the exposure time to Cort was short, the present study cannot rule out that high preoperative exogenous concentrations of Cort increased vascular reactivity [31] and, as a consequence, attenuated vasopressor responses (ie, catecholamines release) to surgery.

In the present study, the early hyperglycemic response to surgery was not increased in rats given preoperative Cort; rather, it was reduced. Thus, our results indicate that Cort is not the primary mediator of early postoperative hyperglycemia. In addition, as shown in Fig. 1, acute increases in plasma Cort in nonstressed animals do only increase plasma glucose at supraphysiologic levels in the Wistar rat.

The combination of postoperative hyperglycemia and hyperinsulinemia in rats that received Veh suggests an increased hepatic glucose production and intact glucose-stimulated insulin release from the β-cell after surgery, but could also reflect a state of extrahepatic insulin resistance. However, rapid changes in plasma glucose are due to hepatic glycogen breakdown and glucose release into the systemic circulation [32]. Therefore, the rapid onset and transient nature of hyperglycemia after surgery in this model suggest that changes in blood glucose levels in all groups of animals were due to increased hepatic glucose output. Sympathetic activation is involved in the development of postoperative hyperglycemia [33,34]. In the present study, the reduced hyperglycemic response by Cort was most likely due to a reduction in sympathetic-stimulated hepatic glucose output after surgery.

In summary, a preoperative 2-hour exposure of physiologic poststress Cort concentrations not only suppressed plasma IL-6 levels but also inhibited surgery-induced adrenaline release and suppressed plasma glucose levels. We hypothesize that glucocorticoids attenuated the inflammatory response in injured tissues, which reduced afferent input into brain areas regulating the neuroendocrine response.

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