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Modulation of host defense by hydrocortisone in stress doses during endotoxemia

Abstract *Objective:* To investigate the effects of low-dose hydrocortisone (HC) on neutrophil respiratory burst, phagocytosis, and elimination of *E. coli* from blood and tissue under endotoxemic and non-endotoxemic conditions. *Design:* Randomized, controlled trial. *Setting:* Experimental laboratory, university hospital. *Subjects:* Forty-eight female chinchilla rabbits (n=8 in six groups A–F). *Interventions:* In order to quantify the bacterial clearance process, defined numbers [10^8 colony forming units (CFU)] of *Escherichia coli* were injected intravenously into all anesthetized rabbits. Group A did not receive further intervention. Group B received bolus administration of HC 1.4 mg/kg and group C 14 mg/kg. Endotoxin (LPS, 40 µg/kg/h) was given to groups D, E, and F. Group E received additional bolus administration of HC 1.4 mg/kg and group F 14 mg/kg. All HC groups (B, C, E, and F) were continuously infused with HC 0.18 mg/kg/h. *Measurements:* Monitored parameters were neutrophil respiratory burst and phagocytosis activity, rates of bacterial elimination from the blood, arterial blood pressure, serum lactate and LPS concentrations, as well as nitrite and nitrate levels. Tissue samples of liver, kidney, spleen, and lung were collected for bacterial counts. *Main results:* In controls HC significantly delayed elimination of injected *E. coli* from the blood (P<0.01). LPS also prolonged bacterial elimination but additional HC did not further delay removal of *E. coli* from the blood. Under endotoxemia HC depressed respiratory burst, whereas phagocytosis functions remained unaltered. Moreover, bacterial colonization of organs was reduced after HC in the LPS groups. Significance, however, was reached only in the liver (P<0.05). Due to HC, clearance from LPS (P<0.01) and lactate (P<0.05) were improved. Levels of nitrite and nitrate did not differ among the groups. *Conclusion:* HC demonstrated immunomodulatory effects even in stress doses. In endotoxemic states use of low-dose HC seems to be favorable, although not in non-septic conditions.

Keywords Hydrocortisone · Respiratory burst · Phagocytosis · Neutrophils · Bacterial killing · Sepsis

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Introduction

In the past 20 years, high doses of corticosteroids (up to 120 mg/kg/day methylprednisone) failed to improve outcome in patients with sepsis (for review, see [1]). Recent investigations, however, showed an adrenocortical function impairment [2] based on a relative cortisol deficiency [3] and a positive influence of hydrocortisone in stress doses (0.18 mg/kg/h) on pro-inflammatory reactions in SIRS [4] and on the clinical course in sepsis and

MOF [5, 6], thus indicating clinical significance (for review see [7]).

Glucocorticoids inhibit transcription and translation of different pro-inflammatory cytokines such as IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, TNFα, and GM-CSF [8] via NFκB-dependent pathways. IL-1ra- and IL-10 generation, however, seems to be unaffected [9]. Most recent data from patients with septic shock indicate that hydrocortisone (10 mg/h) blocks both the pro- and the anti-inflammatory response [10].

Favorable effects of corticosteroids on vascular tone and inflammation in critically ill patients may, however, be counterbalanced by immunosuppressive effects, particularly on neutrophils (PMN), increasing infection rates and, thus, may worsen the outcome.

We hypothesized that hydrocortisone even in stress doses might affect host defense [3, 4, 5]. Hence, we investigated bacterial killing and neutrophil function in a defined experimental setting in endotoxemic (LPS) rabbits [11, 12] under low-dose hydrocortisone infusion. Additionally, systemic endotoxin clearance function was assessed in short intervals. Lactate was quantified as a marker of anaerobic tissue conditions and nitrite and nitrate for determination of potential involvement of inducible NO-synthase [13].

Material and methods

Animal model

Forty-eight female chinchilla rabbits weighing between 2 kg to 3 kg were anesthetized with ketamine (Ketanest, Parke Davis, Germany, 50 mg/kg bw) and xylazine (Rompun, Bayer, Germany, 4 mg/kg bw) and were anticoagulated with heparin-sodium (1,000 IE/kg bw) injected into an ear vein catheter. The animals were placed in a supine position on a temperature-controlled (35 °C) operating table. After tracheotomy and intubation, the rabbits were mechanically ventilated with room air (tidal volume 30 ml, frequency 30/min) via a respirator (Servo ventilator 900D, Siemens-Elema, Solna, Sweden) during the entire observation period. Appropriate ventilation and oxygenation was assured by intermittent blood gas analysis (288 Blood Gas System, Ciba-Corning, Fernwald, Germany). A PVC catheter (1.4 mm) was inserted into the right carotid artery for measurements of the arterial blood pressure and for collection of blood samples. While monitoring the hemodynamic condition anesthesia was maintained by injection of ketamine (5–10 mg/kg/h) and xylazine (0.5–1.5 mg/kg/h). In addition to the basal fluid requirement of 3–4 ml/kg bw, blood loss from sampling was replaced by isovolemic injection of isotonic saline.

Experimental protocol

Following a 30-min period of stable hemodynamics first blood samples were collected for baseline measurements and 48 animals were randomly assigned to six respective groups (Fig. 1): without hydrocortisone treatment (groups A and D), treatment with two different hydrocortisone concentrations (groups B, C, E, and F), without endotoxemia (groups A–C), and 60 min after induction of endotoxemia (groups D–F).

	groups		t=-60 min	t=0 min	t=180 min
A	controls n=8	*E.coli*		10^8 CFU *E. coli*	
		NaCl 0.9%			
		NaCl 0.9%			
B	HC low n=8	*E.coli*		10^8 CFU *E. coli*	
		hydrocortisone	1.4 mg/kg bw & 0.18 mg/kg bw/h →		
		NaCl 0.9%			
C	HC high n=8	*E.coli*		10^8 CFU *E. coli*	
		hydrocortisone	14 mg/kg bw & 0.18 mg/kg bw/h →		
		NaCl 0.9%			
D	LPS n=8	*E.coli*		10^8 CFU *E. coli*	
		NaCl 0.9%			
		LPS	40 µg/kg bw/h →		
E	LPS & HC low n=8	*E.coli*		10^8 CFU *E. coli*	
		hydrocortisone	1.4 mg/kg bw & 0.18 mg/kg bw/h →		
		LPS	40 µg/kg bw/h →		
F	LPS & HC high n=8	*E.coli*		10^8 CFU *E. coli*	
		hydrocortisone	14 mg/kg bw & 0.18 mg/kg bw/h →		
		LPS	40 µg/kg bw/h →		

Fig. 1 Overview of experimental groups and doses. Hydrocortisone (*HC*), endotoxin (*LPS*), colony-forming units (*CFU*)

In all animals the standardized amount of *E. coli* (10^8 CFU) was injected into the ear vein catheter after saline had been infused over a 60-min period (0.1 ml/min). Endotoxemia (groups D–F) was induced by continuous infusion of 40 µg/kg bw/h for the duration of the experiment. In the respective groups hydrocortisone was added in two different bolus concentrations [either 1.4 mg/kg (groups B and E) or 14 mg/kg (groups C and F)] followed by an uniform continuous infusion of 0.18 mg/kg bw/h [5].

For bacterial analysis arterial blood was aseptically drawn at 1 min, 5 min, 15 min, 30 min, 45 min, 60 min, 90 min, 120 min, 150 min, and 180 min after bacterial injection. Blood gases and leukocyte counts were determined at 30-min intervals. PMN oxidative burst and phagocytosis activity were determined before, and at 5 min, 30 min, 90 min, and 180 min after the *E. coli* injection. At the end of the experiment (after 240 min) the animals were killed with ketamine and xylazine. Subsequently, tissue samples of liver, spleen, kidney, and lung were collected under aseptic conditions for bacterial cultures.

Bacterial inoculum

An encapsulated, serum-resistant, non-hemolytic strain of *E. coli* (O111) with a smooth LPS phenotype from the blood of a septicemic patient, was adjusted to a density of 10^8 colony-forming units (CFU)/ml, and frozen in aliquots at −70 °C until use. The amount of 10^8 CFU *E. coli* used in the current study was based on previous experiments [11, 12] providing a reproducible clearance rate and organ distribution without inducing severe hemodynamic disturbances. In control animals, the injection of 10^8 CFU *E. coli* was completely cleared from the circulatory system within a time period of 60 min to 90 min, thus, allowing the registration of acceleration or impairment of the clearance kinetics in the different experimental groups.

Hydrocortisone

A stock solution of 100 mg sodium-hydrocortisone-21-hydrogen-succinate powder (Pharmacia & Upjohn, Erlangen, Germany) with 2 ml of benzyl alcohol was further diluted with sterile saline (48 ml) to a final concentration of 2 mg/ml [4, 5].

PMN burst activity

Intracellular oxygen radical production was determined in 2×100 µl of freshly drawn heparinized whole blood by means of a

commercially available test kit (Bursttest, Orpegen Pharma, Heidelberg, Germany), as previously described [11, 12]. Fifteen thousand cells of each sample were measured with a laser flow cytometer (FACScan/ Lysis II Becton Dickinson, Heidelberg, Germany) using blue-green excitation light (488 nm Argon Laser).

PMN phagocytosis activity

According to previous work [11, 12], a test kit (Phagotest, Orpegen Pharma) was used for determining the phagocytic activity of leukocytes in whole blood (2×100 µl) by measurement of the content of FITC-marked *E. coli* in the phagocytic cells. Data acquisition by flow cytometer was performed in the same manner as in the burst-assay.

Quantitative microbiology

Blood and tissue samples were chilled and assayed in duplicates at the end of the experiment. After incubation of the cultures at 37 °C for 24 h, CFU of *E. coli* were counted. The final bacterial concentration was calculated as the numbers of colonies per milliliter of blood, or as colonies per gram of tissue.

Blood cultures

Blood samples were serially diluted in sterile saline. One hundred microliters each of whole blood and of blood in the various states of dilution were plated onto CLED (cysteine lactose electrolyte deficient)-agar plates according to Sandys [14].

Organ cultures

Aseptically collected organs, liver, spleen, lung, and kidney were weighed, and 0.8–2 g of each organ were homogenized (Ultra-Turrax, IKA, Staufen, Germany) in 3 ml of sterile saline. Serial dilutions of tissue suspension (100 µl) were plated onto CLED agar plates.

Detection of endotoxin

In order to take into account plasma-related factors that interfere with the *Limulus* amebocyte lysate-endotoxin reaction, and considering the fact that each plasma sample when spiked with endotoxin follows a different slope in the standard curve, an automated, kinetic, turbidimetric microtiter test with individual internal standardization was used as previously described [11, 12, 15]. The sensitivity of this assay is 0.1 pg/ml.

Measurement of nitrite and nitrate (NO_x)

A commercially available colorimetric test kit was used for the determination of total NO_x concentration in a two-step process (Cayman Chemicals, Ann Arbor, Mich., USA), after deproteination with methanol. In the first step nitrate was converted into nitrite utilizing nitrate reductase. As a second step, Griess reagent [16] was added which converts nitrite into a deep purple azo-compound. A photometric measurement (AR 2001, Anthos, Krefeld, Germany) of the light absorption at 540 nm due to this azo chromophore determines the NO_2 concentration. Azide, ascorbic acid, dithiothreitol, and mercaptoethanol interfere with the color development in concentrations of 100 µM, and phosphate >50 mM interferes with the conversion of nitrite to nitrate.

Lactate measurement

Lactate concentration was measured enzymatically by means of an automatic amperometric system (LACT MPR1, Boehringer, Mannheim, Germany) according to the manufacturer's instructions (Analyser ESAT 6661 Lactat, Eppendorf, Germany) in the Institute for Clinical Chemistry, University Hospital, Mannheim, Germany.

Statistical analysis

Data are presented as the arithmetic mean±standard deviation (SD). The logarithm of bacterial counts was used for statistical comparison. A repeated measurement analysis of the group factors (e.g., bacterial blood cell counts over time and groups) was performed by general linear model statistics (GLM), according to a two-way analysis of variance. One-way analysis of variance (ANOVA) was used for comparing one group to another after single measurements (e.g., organ colonization over groups). All multiple comparisons were followed by a Bonferroni correction. Statistical significance was accepted for all procedures at $P<0.05$. Statistical analysis was performed with SPSS software for MS Windows (Release 10.0.7, SPSS, Chicago, Ill., USA).

This study was approved by the Animal Subject Protection Committee of the local government. The care and handling of animals were in accordance with the principles expressed in the Helsinki Declaration.

Results

Bacterial elimination from blood and tissues

Compared to controls (group A; Fig. 2A,B) endotoxemia (group D) resulted in a significantly prolonged bacterial clearance (P=0.001). Moreover, LPS injection induced a significantly higher *E. coli* colonization (P=0.018–0.033) in all organs.

In contrast to the endotoxemic groups (D–F), in which no statistical difference between hydrocortisone administration (E, F) and LPS-controls (D) could be detected (Fig. 2B), bacterial clearance in both hydrocortisone groups without endotoxemia (B, C) was significantly prolonged, compared to controls (A; Fig. 2A; $P<0.001$).

Bacterial organ colonization (Fig. 2C,D) without endotoxemia (groups A–C) did not differ between the groups, whereas endotoxemic animals (groups D–F) showed an altered*E. coli* distribution in the liver with regard to hydrocortisone. High-dosage hydrocortisone application (group F) resulted in a significant reduction of liver colonization (P=0.028). The reduction in lung colonization, however, failed to reach statistical significance in the hydrocortisone/LPS groups E and F.

Endotoxin concentrations after 60 min of endotoxemia were 55.2±43.4 ng/ml. Both concentrations of hydrocortisone resulted in significantly improved LPS blood clearance (Fig. 3; $P<0.01$).

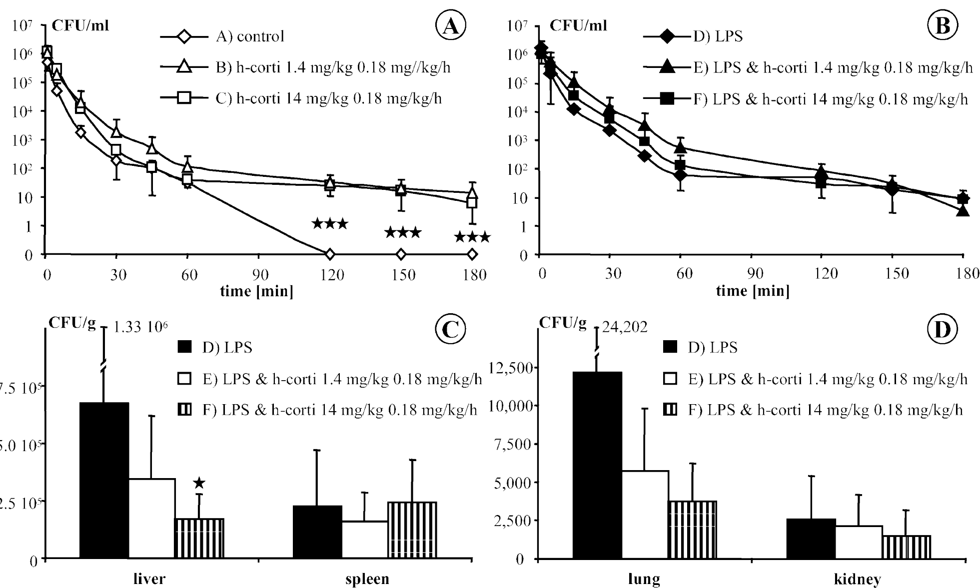

Fig. 2A–D **A** Bacterial clearance of 10^8 colony-forming units *E. coli* (CFU/ml±SD, semilogarithmic) from the blood, 60 min after hydrocortisone application (14 mg/kg bw or 1.4 mg/kg bw) and subsequent continuous hydrocortisone infusion (0.18 mg/kg bw/h) in respective groups. Controls without hydrocortisone (***P<0.001 control vs high- and low-dose hydrocortisone, *GLM*); **B** Additional endotoxin (*LPS*) infusion 40 µg/kg bw/h 60 min prior to bacteria application; **C**, **D** Organ colonization 180 min after i.v. injection of 10^8 colony-forming units (CFU/g±SD) of *E. coli*. All animals received LPS infusion (40 µg/kg bw/h) 60 min prior to bacteria application. Hydrocortisone boluses (14 mg/kg bw or 1.4 mg/kg bw) were administered 60 min prior to *E. coli*, followed by continuous hydrocortisone infusion (0.18 mg/kg bw/h) in respective groups. Controls received no hydrocortisone (*P<0.05 LPS vs LPS & high-dose hydrocortisone; ANOVA)

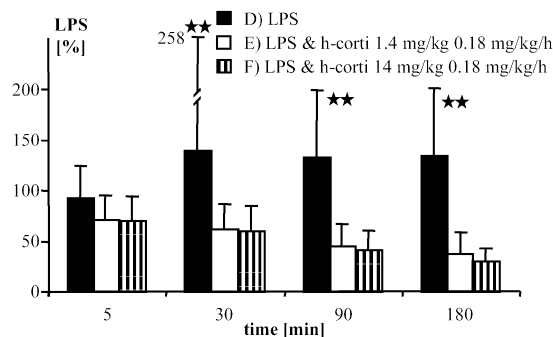

Fig. 3 Endotoxin (*LPS*) clearance±SD (percentage of baseline 0 min) after i.v. injection of 10^8 colony-forming units of *E. coli*. All animals received LPS infusion (40 µg/kg bw/h) 60 min prior to bacteria application until 180 min. A hydrocortisone bolus (14 mg/kg bw or 1.4 mg/kg bw) was administered 60 min prior to *E. coli*, followed by continuous hydrocortisone infusion (0.18 mg/kg bw/h) in respective groups. Controls received no hydrocortisone. **P<0.01 LPS vs LPS & hydrocortisone in both doses; GLM

White blood cell counts and PMN function

Preceding any intervention. the mean total white cell count was 5,384±1,956 Pt/µl, including 2,594±1,248 Pt/µl neutrophils (Fig. 4A, B). In all LPS groups (D, E, F) 1 h of endotoxemia significantly reduced the number circulating neutrophils (P<0.001). In the non-endotoxemic animals (groups A, B, C) the white cell count significantly (P<0.001) dropped 5 min after *E. coli* injection to 721±609 Pt/µl (PMN 14±10 Pt/µl). Compared to groups A and B, the significant drop of neutrophils after *E. coli* was most marked in group C (Fig. 4A) but differential white cell counts showed no significant group differences. The drop of neutrophils after *E. coli* in the groups without endotoxemia (A–C) was accompanied by an 11.9±5.0-fold increase in respiratory burst 5 min after the *E. coli* injection (Fig. 5A), which was not statistically significant. In endotoxemic animals, however, PMN counts (Fig. 4B) already dropped in response to LPS, and respiratory burst (Fig. 5B) was significantly depressed in both hydrocortisone groups (E, F; P<0.05). Phagocytosis activity, expressed as mean fluorescence intensity per cell, did not show any significant hydrocortisone dependent effects (Fig. 5C, D).

Hemodynamic effects and nitric oxide interactions

While in controls mean arterial pressure dropped from 50±13 mmHg to 28±5 mmHg after 180 min, hydrocortisone significantly stabilized hemodynamics (P=0.033) with mean arterial pressures of 44±10 mmHg (low-dose hydrocortisone) and 42±8 mmHg (high-dose hydrocortisone) after 180 min. This was associated with a significantly reduced serum lactate concentration in the LPS group with low-dose hydrocortisone application (Fig. 6B;

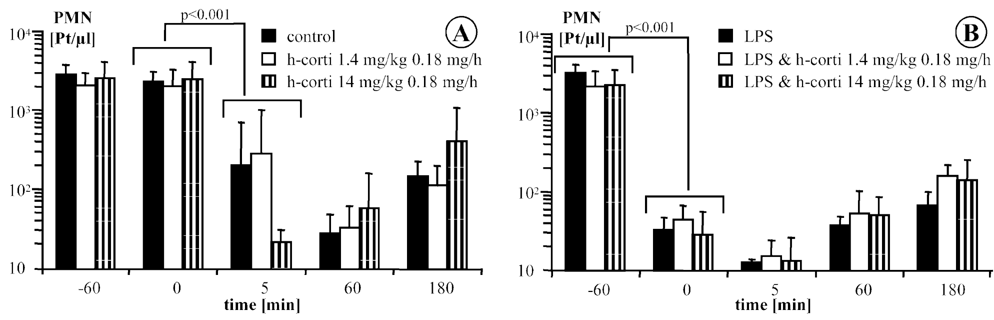

Fig. 4A, B **A** Neutrophil (PMN) count±SD (semilogarithmic) before (−60 min, 0 min) and after i.v. injection of 10^8 colony-forming units *E. coli*, 60 min after a hydrocortisone bolus (14 mg/kg bw or 1.4 mg/kg bw), and subsequent continuous hydrocortisone infusion (0.18 mg/kg bw/h) in respective groups. Controls received no hydrocortisone; **B** Additional LPS infusion 40 µg/kg bw/h −60 min until 180 min

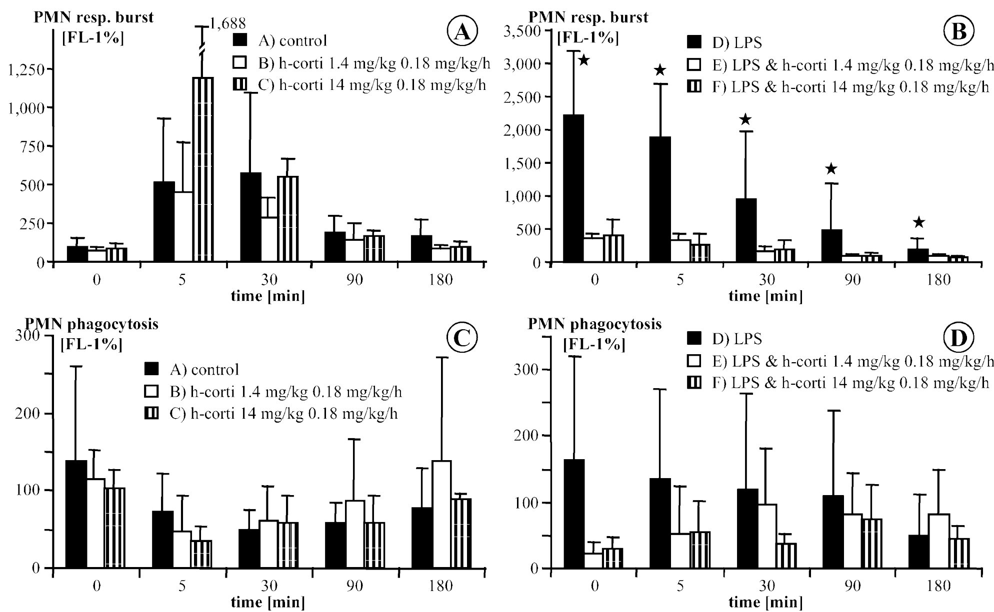

Fig. 5A–D **A** Neutrophil (*PMN*) respiratory burst±SD (percentage of baseline −60 min) after i.v. injection of 10^8 colony-forming units *E. coli*, 60 min after a hydrocortisone bolus (14 mg/kg bw or 1.4 mg/kg bw) and subsequent continuous hydrocortisone infusion (0.18 mg/kg bw/h) in respective groups. Controls received no hydrocortisone; **B** Additional LPS infusion 40 µg/kg bw/h 60 min prior to bacteria application (*P<0.05 LPS vs high- and low-dose hydrocortisone GLM); **C** Phagocytosis of FITC marked *E. coli* by PMN±SD (percentage of baseline −60 min) after i.v. injection of 10^8 colony-forming units *E. coli*, 60 min after a hydrocortisone bolus (14 mg/kg bw or 1.4 mg/kg bw) and subsequent continuous hydrocortisone infusion (0.18 mg/kg bw/h). Controls received no hydrocortisone; **D** Additional LPS infusion 40 µg/kg bw/h 60 min prior to bacteria application

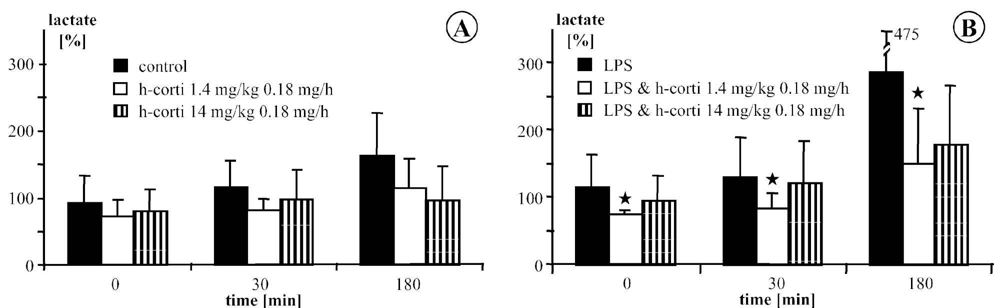

Fig. 6A, B **A** Percentage serum lactate concentration±SD of baseline (−60 min) after i.v. injection of 10^8 colony-forming units *E. coli*, 60 min after a hydrocortisone bolus (14 mg/kg bw or 1.4 mg/kg bw) and subsequent continuous hydrocortisone infusion (0.18 mg/kg bw/h). Controls received no hydrocortisone. Lactate percentages in relation to $t = -60$ min, prior to intervention; **B** Additional endotoxin (*LPS*) infusion 40 µg/kg bw/h 60 min prior to bacteria application (*P<0.05 LPS vs LPS & low-dose hydrocortisone)

$P<0.05$). Baseline serum lactate concentrations were 3.1±2.4 mmol/l. The group differences in serum lactate found after endotoxemia (Fig. 6B) were not statistically significant in groups without LPS application (Fig. 6A).

To control hydrocortisone interaction with NO-synthesis activity, nitrate and nitrite were measured as stable NO metabolites with baseline values of 25.0±8.7 μmol/l. During the entire observation period no major changes were detectable within or between the groups.

Discussion

Recent studies in patients with septic shock showed favorable effects of hydrocortisone in "stress substitutional doses" [4, 5, 6, 10]. Our goal was to evaluate the effects of different doses of hydrocortisone (Fig. 1) on bacterial and LPS clearance as well as on phagocytosis and lytic function of neutrophils as an essential part of the cellular immune defense system. Hence, blood bacteria clearance and colonization of different organs in controls and in endotoxemia with or without hydrocortisone were measured. We chose hydrocortisone doses described by Briegel [4, 5] as physiological stress doses, and a tenfold higher concentration in two additional experimental groups. To be able to establish a correlation between cellular resistance mechanisms and blood and tissue bacterial killing we subsequently evaluated granulocyte phagocytosis and burst activity alongside microbiological parameters.

In line with prior experiments in the same animal model [11, 12], endotoxemia prolonged blood bacterial clearance and induced a higher organ colonization. These observations were attributed to a preloading or preexhaustion of the mononuclear phagocyte system [17].

In non-endotoxemic animals treatment with hydrocortisone significantly extended bacterial clearance (Fig. 2A). This hydrocortisone effect may not, however, be explained with the data of PMN burst activity (Fig. 5A) or phagocytosis (Fig. 5C), which remained unaltered. In contrast, LPS-induced prolongation of bacterial clearance did not further change in response to hydrocortisone (Fig. 2B), whilst significant suppression of PMN-burst was present (Fig. 5B). Phagocytosis (Fig. 5D), however, was not suppressed by hydrocortisone in endotoxemic animals. These findings are concordant with the observation of reduced oxidative PMN- burst after 100 mg hydrocortisone in humans [18] and increased infection rates of earlier studies with higher doses of hydrocortisone [1]. At first glance the differential effects of the applied doses of hydrocortisone on respiratory burst (reduced) and phagocytosis (unaltered) appear puzzling. However, phagocytosis and respiratory burst are two different mechanisms of host defense. They may be affected independently, since phagocytosis is more an issue of cytoskeletal factors [19] while respiratory burst is more reliant on oxidases [20] or NO-synthases [21]. The sequel of both mechanisms, however, is crucial for effective host defense. On the other hand, supra-effective activation of the discussed neutrophil functions induces host tissue damage [22]. Thus, overflow limitation of inflammation, while maintaining an *adequate* immune-response, is a key issue in severe illness. One possible interpretation of the observed discrepancy of reduced burst (Fig. 5B) and unaltered bacterial elimination (Fig. 2B) during endotoxemia might be that whenever the killing effect of oxygen radicals has reached a saturation point, increases in radical-concentrations (D: 22-fold vs E, F 3.5–4-fold) do not quantitively improve bacterial killing any further. This could result in a tissue protective effect of low-dose hydrocortisone by reducing an overwhelming phagocyte activation and, hence, tissue damage [8, 24]. This effect may explain the observed reduction of the bacterial organ colonization in the liver (Fig. 2C). Lack of significant statistical data regarding lung tissue could in part be a consequence of hepatic effects as a "prepulmonary bacterial filter".

The significantly accelerated blood endotoxin clearance (Fig. 3), seems to confirm the theory that low-dose hydrocortisone reduces tissue damage and improves tissue perfusion, which has clinical relevance in the prognosis of survival after severe trauma [23]. With regard to LPS, reduced tissue damage might also result from glucocorticoid-dependent suppression of monocyte-activation via the lipopolysaccharide receptor antigen CD14 [24]. Further tissue preservation could originate from the blockade of group II phospholipase A_2 expression [25], cyclooxygenase-2 induction [26], and endothelin-1 production [27].

Reduced lactate concentrations under hydrocortisone application during endotoxemia (Fig. 6B) further indicate, besides improved tissue oxygenation with significantly higher systemic blood pressures, an improved hepatic lactate clearance, which might result from hydrocortisone-mediated liver protection. In addition, improvement of the hemodynamic situation may be due to advantageous effects of hydrocortisone on vascular responsiveness [5] in terms of increasing the sensitivity of adrenoreceptors [28, 29].

In patients with septic shock stabilizing effects of hydrocortisone on blood pressure were attributed to reduced levels of nitric oxide [10], due to suppression of the inducible form of nitric oxide synthase, which plays a key role in volume resistant hypotension [30, 31]. In the clinical setting, however, this effect of hydrocortisone was not demonstrated until after 24 h [10]. The delayed onset may be explained by the observation that iNOS-mRNA could not be detected until 2 h after shock induction and reached peak values between 6 h and 12 h [30]. Recent data [32, 33] question the value of plasma-NO_x measurements for the assessment of iNOS- derived NO-generation, since NOS-independent factors influence NO_3-concentrations. The relatively long half-life of NO_3 might also have contributed to the failure to detect time- or

group-dependent changes within our observational window. Accordingly, in a model of porcine endotoxemia, Matejovic could not detect differences in plasma NO_x-concentrations despite the fact that exhaled NO significantly differed after 18 h of LPS [32]. Moreover, Pastor showed elevated iNOS expression after LPS but unaltered plasma NO_x levels [34]. The unchanged concentrations of the NO metabolites nitrite and nitrate in the hydrocortisone group do not inevitably exclude down-regulation of iNOS expression [32, 34]. They might rather be attributed to the short observation interval of 4 h. Besides the discussed effects, improved cellular barrier functions [35] or sodium channel-dependent effects favoring sodium reabsorption [36] under glucocorticoid application could counterbalance intravascular hypovolemia and therefore stabilize hemodynamics. Thus, the present animal model does not allow conclusions about the definite mechanisms of the significantly elevated blood pressure after hydrocortisone administration.

The current data were obtained from an endotoxemia model with an early treatment approach, which shares some features of pre-treatment. Although there are limitations in comparability with the clinical situation in human septic shock, this approach permits a standardized observation. Nevertheless, conclusions may be drawn from this model, when low-dose hydrocortisone administration may have beneficial effects on host defense and when unfavorable effects may be encountered.

Conclusions

In summary, the applied hydrocortisone doses and their effects seem to be cutting both ways in this animal model. On the one hand, the anti-inflammatory effect of hydrocortisone in a healthy organism prolongs bacterial blood clearance. In endotoxemia, on the other hand, hydrocortisone ensues an organ protective function by modulating pro-inflammatory reactions especially in the liver, improving bacterial, LPS, and lactate clearance. These findings show that hydrocortisone already has an immune modulating effect in high physiological concentrations. Favorable effects of low-dose hydrocortisone were observed in endotoxemic states, although not under non-septic conditions.

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