

# Gastroprotective action of glucocorticoids during the formation and the healing of indomethacin-induced gastric erosions in rats

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## Abstract

The aim of the present study consisted of the investigation of glucocorticoid role in the formation and the healing of indomethacin-induced (25 mg/kg, sc) gastric erosions in rats. The effect of deficiency of glucocorticoid production followed by corticosterone replacement on the formation and the healing of the gastric erosions was evaluated. Glucocorticoid production was decreased by adrenalectomy or by delayed inhibitory action after a single pharmacological dose of cortisol (300 mg/kg ip) injected 1 week before the onset of ulcerogenic stimulus. Indomethacin induced corticosterone rise and caused gastric erosions. The loss of indomethacin-induced plasma corticosterone rise potentiated the formation of indomethacin-induced erosions in both models. The area of gastric erosions in rats with glucocorticoid deficiency was considerably larger than that in control animals 4 h after indomethacin administration as well as during 48 h after the drug administration (period of erosion healing). Injecting corticosterone in rats with glucocorticoid deficiency significantly decreased the formation of indomethacin-induced gastric erosions and promoted their healing. Thus, the present data support the gastroprotective action of glucocorticoids in the formation and in the healing of indomethacin-induced mucosal injury. © 2001 Elsevier Science Ltd. All rights reserved.

*Keywords:* Gastric erosions; Indomethacin; Glucocorticoids; Adrenalectomy

## 1. Introduction

According to the widely held view based on the notion about ulcerogenic properties of large amount of exogenous glucocorticoids, glucocorticoids released during activation of hypothalamic-pituitary-adrenocortical (HPA) axis are harmful for the stomach. As the notion about pathogenic ulcerogenic role of endogenous glucocorticoids is difficult to reconcile with the adaptive role HPA axis hormones, a few years ago we set out to clarify the validity of the view about ulcerogenic action of endogenous glucocorticoids. Our previous results obtained from a variety of experimental approaches point to the opposite direction, i.e. the acute rise of glucocorticoid production protects gastric mucosa against erosion formation. In previous studies we re-evaluated the role of endogenous glucocorticoids in stress-induced gastric ulceration and showed that glucocorticoids released during stress have a gastroprotective action against stress-induced gastric damage [5–8].

In the present study, we investigated whether glucocorticoids have gastroprotective action against formation of gastric mucosal injury caused by indomethacin. It is well known that this non-steroidal anti-inflammatory drug (NSAID) produces gastric mucosal injury in experimental animals [18,24] and humans [12,15,28]. Moreover, in accordance with our previous results, indomethacin administration also induced a plasma corticosterone rise.

Another aim of the present study was to elucidate the glucocorticoid role in the healing of gastric mucosal injury caused by indomethacin. In accordance with data of literature [3,13,14,16], glucocorticoids injected into animals at pharmacological doses delay the natural healing of experimental gastric injury. We were interested in the role of endogenous glucocorticoids as well as the exogenous ones injected at physiological replacement doses in the healing of gastric mucosal injury.

So, the present study was performed to investigate the role of glucocorticoids in the formation and the healing of indomethacin-induced gastric erosions. For these aims we evaluated the effect of deficiency of glucocorticoid production followed by corticosterone replacement on the formation and the healing of the gastric erosions caused by indomethacin.

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## 2. Materials and methods

### 2.1. Animals and housing conditions

Adult male Sprague–Dawley rats weighing about 250 g were used. Five animals were housed per cage, and animals were acclimatized to standard laboratory conditions (12:12-h light–dark cycle, temperature  $20 \pm 1$  °C, free access to food and water) for 7 days before use. In all experiments the animals were deprived of food but not water for 24 h before indomethacin administration and for 4 h after it. Grid floors were placed in the home cages to prevent coprophagy.

### 2.2. Gastric mucosal injurious agent and estimation of gastric erosions

Indomethacin (Sigma, Steinheim, Germany) was used as gastric mucosal injurious agent and was prepared freshly for each experiment. Indomethacin was injected subcutaneously at a dose of 25 mg/kg. The drug was suspended in saline with a drop of Tween 60 (Theodor Schuchardt, Munchen, Germany) and injected sc in a volume of 5 ml/kg. Control rats were injected saline (5 ml/kg).

Rats were decapitated 4, 7, 12, 24 and 48 h after indomethacin injection. The stomachs were removed and filled with 10 ml of saline. Thirty minutes later, each stomach was opened by cutting along the greater curvature, cleaned, and spread. The stomach was examined with a video camera system permitting measurement of the area of lesion [9], or with a binocular dissection microscope. The area of each lesion was measured in square millimeters, and the cumulative area of all lesions in a rat served as the measure of erosion damage.

### 2.3. Blood sampling and hormone measurements

Trunk blood for measurement of corticosterone levels was collected after decapitation of rats 4, 7, 12, 24 and 48 h after indomethacin injection. In Experiment 1, blood was collected through indwelling venous cannula (placed 1 day earlier) before and during 4 h after indomethacin administration. Blood samples (0.3 ml) were replaced by an identical volume of physiological saline. Our previous study [7] has shown that the sampling procedure did not change plasma corticosterone levels. The blood samples were centrifuged at 4 °C, and the plasma was frozen for hormonal analysis.

Corticosterone level of plasma was measured by microfluorometry [2]. Using this methods the background fluorescence is equivalent to 4–6 µg/100 ml corticosterone and data were not corrected for this background. Intra- and interassay variation of measurements was 5.1 and 7.4%, respectively.

### 2.4. Surgical methods

All rats were surgically manipulated under pentobarbital anesthesia (45 mg/kg Nembutal; Serva, Heidelberg, Germany). Rats were adrenalectomized through a lateral incision below the last rib 1 week before administration of indomethacin. Sham operated rats were subjected to the same surgical procedure, but adrenals were not removed. After surgery, adrenalectomized rats were provided with 0.9% NaCl solution in addition to tap water in the home cage.

A Silastic cannula was placed into the right atrium through the right jugular vein and exteriorized through a small incision at the back of the neck.

### 2.5. Treatment protocol

#### 2.5.1. Experiment 1: effect of indomethacin on plasma corticosterone level in cannulated rats with intact adrenals

Corticosterone levels were measured before and during 4 h after indomethacin injection as well as after administration of its vehicle.

#### 2.5.2. Experiment 2: effect of adrenalectomy on the formation of gastric erosions induced by indomethacin

In this experiment we estimated and compared gastric erosions as well as corticosterone responses induced by indomethacin in 4 h after its injection in rats with (1) sham operation, (2) adrenalectomy, (3) adrenalectomy with replacement of corticosterone injected 15 min before indomethacin administration.

Seven days after adrenalectomy one half of the adrenalectomized rats were injected with corticosterone (4 mg/kg in 1 ml/kg 1,2-propylene glycol sc; Serva), the remaining adrenalectomized rats and all sham operated animals were injected the same volume of vehicle. Fifteen minutes after corticosterone or vehicle injection, the animals were administered indomethacin. Four hours after indomethacin administration animals were killed, trunk blood for measurement of corticosterone levels was collected and stomachs were removed for estimating of gastric erosion areas.

#### 2.5.3. Experiment 3: effect of glucocorticoid deficiency caused by cortisol pretreatment on the formation of gastric erosions induced by indomethacin

The decrease in glucocorticoid production was created by delayed action after a single pharmacological dose of cortisol (300 mg/kg bw, ip; 2.5% suspension, 12 ml/kg) injected 1 week before indomethacin administration. The timing of cortisol treatment was chosen so that during indomethacin action the exogenous hormone has already been eliminated but the corticosterone response to indomethacin was still inhibited. Control rats received saline (12 ml/kg bw, ip) 1 week before indomethacin administration.

In this experiment we estimated and compared gastric erosions as well as corticosterone responses induced by indomethacin in 4 h after its injection in rats with (1) saline injection (control), (2) cortisol pretreatment, (3) cortisol pretreatment followed by corticosterone replacement 15 min before the injection of indomethacin.

Seven days after cortisol pretreatment half of the rats were injected with corticosterone (4 mg/kg in 1 ml/kg 1,2-propylene glycol sc; Serva), the other half and all control animals were injected with the same volume of vehicle. Fifteen minutes after corticosterone or vehicle injection the animals were administered indomethacin. Four hours after indomethacin administration animals were killed, trunk blood was collected and stomachs were removed.

#### 2.5.4. Experiment 4: effect of adrenalectomy on the healing gastric erosions induced by indomethacin

In this experiment we estimated and compared gastric erosions as well as corticosterone responses induced by indomethacin in 4, 7, 12, 24 and 48 h after its injection in rats with (1) sham operation, (2) adrenalectomy, (3) adrenalectomy with replacing corticosterone injected in 4 h after indomethacin administration.

Four hours after indomethacin administration, all animals in this experiment as well as those in Experiment 5 had free access to food and water. This time point was taken as the “O” point for the healing process.

Seven days after adrenalectomy and 4 h after indomethacin administration half of the adrenalectomized rats were injected with corticosterone (4 mg/kg in 1 ml/kg 1,2-propylene glycol sc; Serva), the remaining adrenalectomized rats and all sham operated animals were injected with the same volume of vehicle. Four, 7, 12, 24 and 48 h after indomethacin administration animals were killed, trunk blood was collected and stomachs were removed.

#### 2.5.5. Experiment 5: effect of glucocorticoid deficiency caused by cortisol pretreatment on the healing of gastric erosions induced by indomethacin

The decrease in glucocorticoid production by cortisol pretreatment was created as in the Experiment 3.

In this experiment we estimated and compared gastric erosions as well as corticosterone responses induced by indomethacin at 4, 7, 12, 24 and 48 h after its injection in rats with (1) saline injection (control), (2) cortisol pretreatment, (3) cortisol pretreatment followed by replacing corticosterone injected at 4 h after indomethacin administration.

Seven days after cortisol pretreatment and 4 h after indomethacin administration half of the rats were injected with corticosterone (4 mg/kg in 1 ml/kg 1,2-propylene glycol sc; Serva), the other half and all control animals were injected the same volume of vehicle. In 4, 7, 12, 24 and 48 h after indomethacin administration

animals were killed, trunk blood was collected and stomachs were removed.

### 2.6. Statistical analysis

Data are shown as mean  $\pm$  S.E. We used the non-parametric Kruskal–Wallis test followed by Mann–Whitney test for comparing erosion scores. With the corticosterone data we used two-way ANOVA for repeated measures followed by Tukey’s multiple comparison test. The Statistica program (StatSoft, Tulsa, OK) was used for calculations.

## 3. Results

### 3.1. Effect of indomethacin on gastric mucosa and plasma corticosterone level

Four hours after administration indomethacin (25 mg/kg, sc) produced typical haemorrhagic gastric erosions, with an area of damage in the controls ranging from 1.6 to 4.7 in the various series. This variation in the size of lesions is probably due to the various sham procedures applied to the various control groups.

Indomethacin injection in rats with intact adrenals raised plasma corticosterone level, which was still significantly above ( $P < 0.05$ ) the basal corticosterone level at all time points (Fig. 1). Corticosterone level was increased only during the first hour after vehicle injection. Plasma corticosterone level after indomethacin injection was significantly higher than after vehicle injection in all time points (Fig. 1).

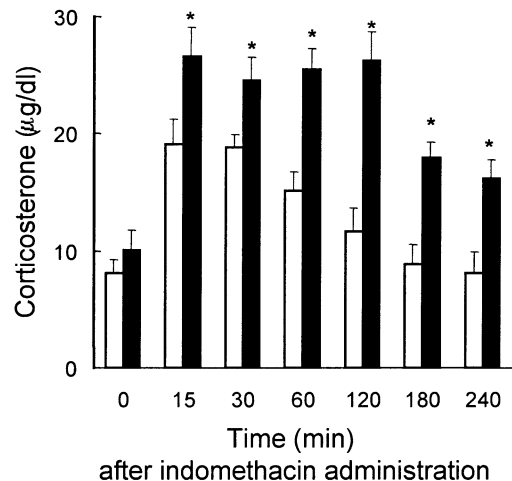


Fig. 1. Plasma corticosterone levels in rats with jugular cannula in response to indomethacin, 25 mg/kg, sc (■) or vehicle (□) injection. Values are means  $\pm$  S.E. from 8–13 rats/group. \* $P < 0.05$  compared with the control group given vehicle. Plasma corticosterone levels measured after indomethacin injection were significantly different from basal levels at all time points ( $P < 0.05$ ). Plasma corticosterone levels measured after vehicle injection were significantly different from basal levels ( $P < 0.05$ ) only at 15, 30, and 60 min after the injection.

### 3.2. Effect of glucocorticoid deficiency followed by corticosterone replacement on the formation of indomethacin-induced gastric erosions

One week after adrenalectomy the corticosterone response to indomethacin injection was prevented (Fig. 2A). Adrenalectomy potentiated gastric erosions induced by indomethacin. The average area of the gastric erosions in adrenalectomized rats was considerably larger than that in sham-operated animals (Fig. 2B). Erosions were not observed in any adrenalectomized rats with vehicle injection. To elucidate whether the absence of acute corticosterone rise was the reason of enhanced erosion formation after adrenalectomy, corticosterone replacement was given to adrenalectomized rats. Corticosterone injected in a dose of 4 mg/kg 15 min before indomethacin mimicked indomethacin-induced corticosterone production in adrenalectomized rats. Replacing corticosterone (4 mg/kg) prevented the erosion-promoting effect of adrenalectomy (Fig. 2B). There were no differences in the area of indomethacin-

induced gastric lesions between adrenalectomized rats with corticosterone replacement and sham operated rats ( $P > 0.5$ ).

One week after cortisol pretreatment corticosterone response to indomethacin injection was also prevented (Fig. 3A) as in the case of adrenalectomy. No pathological changes of gastric mucosa were observed in any rats without indomethacin injection from the 1st to the 7th day after cortisol pretreatment. Indomethacin produced typical gastric erosion in both rats with normal glucocorticoid production (control) and animals with deficient glucocorticoid production (cortisol pretreated). However, the average area of indomethacin-induced erosions in rats with glucocorticoid deficiency was considerably larger than that in control animals (Fig. 3B). Replacing corticosterone (4 mg/kg) significantly decreased the indomethacin-induced erosion formation in cortisol pretreated rats (Fig. 3B). There were no differences in the area of indomethacin-induced gastric lesions between cortisol pretreated rats with corticosterone replacement and control animals ( $P > 0.5$ ).

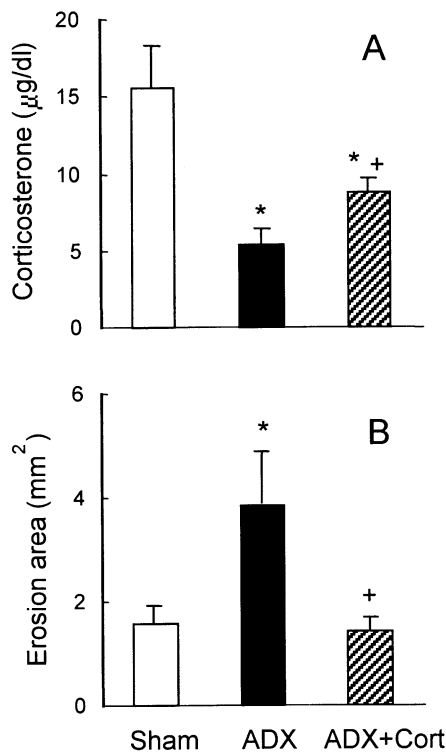


Fig. 2. Effect of adrenalectomy on plasma corticosterone levels (A) and gastric erosions caused by indomethacin injected sc at a dose of 25 mg/kg (B). Seven days before indomethacin rats were sham-adrenalectomized (Sham), adrenalectomized (ADX) or adrenalectomized and later, 15 min before indomethacin, injected with corticosterone (4 mg/kg, sc) (ADX + Cort). On panel A the corticosterone level in the ADX group is equivalent to background fluorescence. Animals were killed 4 h after indomethacin administration. Values are means  $\pm$  S.E. from 9 to 15 animals/group. \* $P < 0.05$  compared with Sham group, + $P < 0.05$  compared with ADX group.

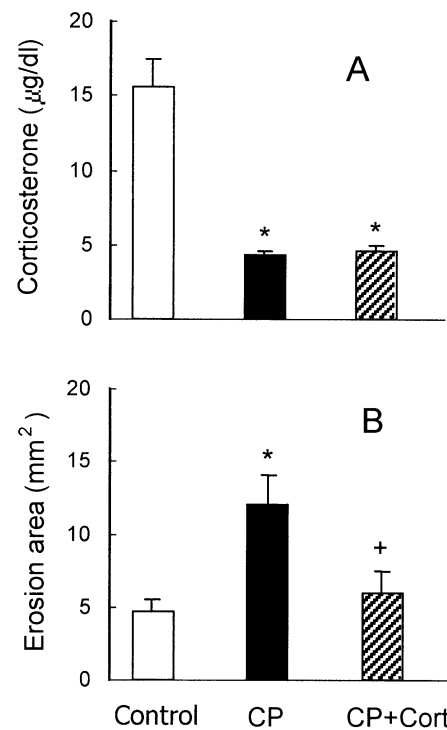


Fig. 3. Effect of cortisol pretreatment (300 mg/kg, ip) on plasma corticosterone levels (A) and gastric erosions caused by indomethacin injected sc at a dose 25 mg/kg (B). Seven days before indomethacin rats were saline pretreated (Control), cortisol pretreated (CP), or cortisol pretreated and later, 15 min before indomethacin, injected with corticosterone (CP + Cort). Injecting corticosterone mimicked corticosterone response to indomethacin during 3 h after the injection and 4 h after the injection an exogenous corticosterone practically disappeared from the plasma. Animals were killed 4 h after indomethacin administration. Values are means  $\pm$  S.E. from 10 to 20 animals/group. \* $P < 0.05$  compared with Control group, + $P < 0.05$  compared with CP group.

### 3.3. Effect of glucocorticoid deficiency followed by corticosterone replacement on the healing of indomethacin-induced gastric erosions

Since in preliminary studies indomethacin-injured gastric mucosa was repaired within 48 h of indomethacin administration, the healing in every experimental group was assessed during this period (7, 12, 24, 48 h after indomethacin administration). The data presented in Fig. 4 show that the effect of adrenalectomy, as well as cortisol pretreatment (carried out one week before indomethacin administration) on glucocorticoid production, was still preserved during 48 h after administration of this ulcerogenic stimulus. At all time points after indomethacin administration corticosterone level

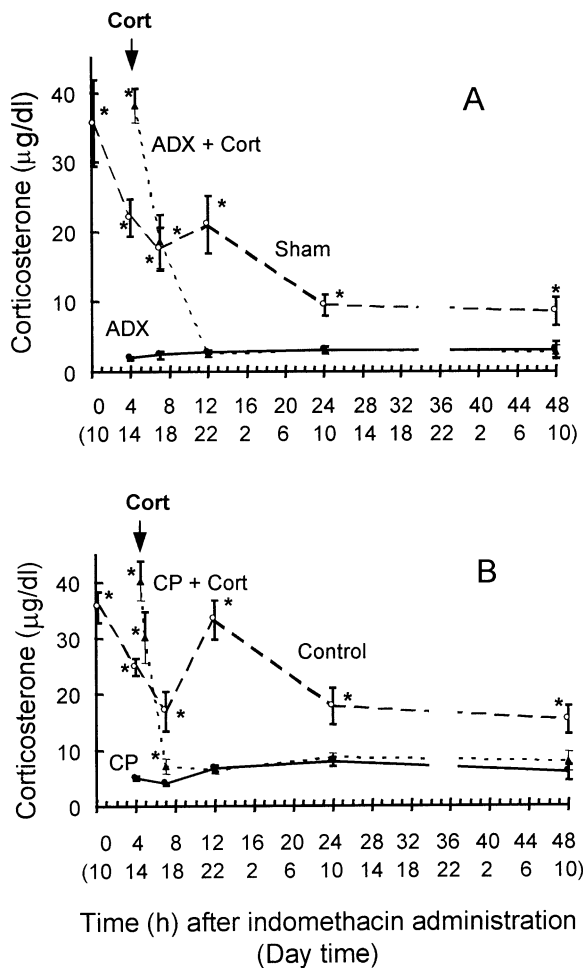


Fig. 4. Plasma corticosterone levels in response to indomethacin (25 mg/kg, sc) in adrenalectomized (A), cortisol pretreated (B) rats without and with injecting corticosterone (Cort). Seven days before indomethacin rats were sham-adrenalectomized (Sham) or saline injected (Control), adrenalectomized (ADX) or cortisol pretreated (CP), adrenalectomized and later, 4 h after indomethacin administration, injected with corticosterone (ADX + Cort) or cortisol pretreated and later, 4 h after indomethacin administration, injected with corticosterone (CP + Cort). Animals were killed 4, 7, 12, 24 and 48 h after indomethacin administration. Values are means  $\pm$  S.E. from 5–6 animals/group. \* $P < 0.05$  compared with ADX (A) or CP (B) group.

in adrenalectomized (Fig. 4A) or cortisol pretreated rats (Fig. 4B) was significantly lower than that in respective (sham or saline) control group. In contrast to control rats, adrenalectomized or cortisol pretreated rats had neither corticosterone reaction to indomethacin administration nor a natural circadian increase in corticosterone level in the evening (22:00), at the beginning of the dark period.

Compared with control rats, the area of gastric erosions in adrenalectomized and cortisol-pretreated rats was considerably larger at 4 h after indomethacin administration as well as 7, 12, 24, and 48 h after the drug administration (Figs. 5 and 6). In both groups of rats with glucocorticoid deficiency, the rate of healing was reduced compared with respective control group. Compared with the time point “4 h after indomethacin administration”, in adrenalectomized rats a significant decrease of erosion areas ( $P < 0.05$ ) have been demonstrated only at 24 h after indomethacin administration, in cortisol pretreated rats it has been found at 12 h, while at the same time in both control groups a significant decrease was observed earlier, at 7 h after indomethacin administration. Moreover, in both control groups there were significant differences ( $P < 0.05$ ) in area of gastric erosions between two time points: 12 h and 48 h after indomethacin administration. At the same time, there were no differences ( $P > 0.5$ ) between these points in adrenalectomized cortisol pretreated rats.

Injection of corticosterone (4 mg/kg) in adrenalectomized or cortisol pretreated rats 4 h after indomethacin administration created plasma corticosterone level that

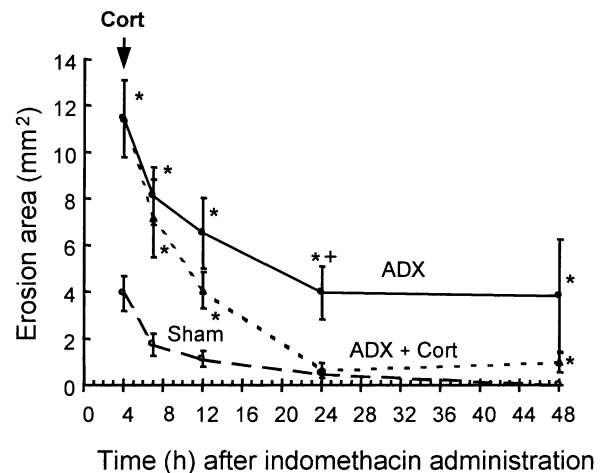


Fig. 5. Effect of adrenalectomy followed by injecting corticosterone (Cort) on the healing of gastric erosions caused by indomethacin administered sc at a dose 25 mg/kg. Seven days before indomethacin rats were sham-adrenalectomized (Sham), adrenalectomized (ADX) or adrenalectomized and later, 4 h after indomethacin administration, injected with corticosterone (ADX + Cort). Animals were killed 4, 7, 12, 24 and 48 h after indomethacin administration. Values are means  $\pm$  S.E. from 5–16 animals/group. \* $P < 0.05$  compared with Sham group, + $P < 0.05$  compared with ADX + Cort group.

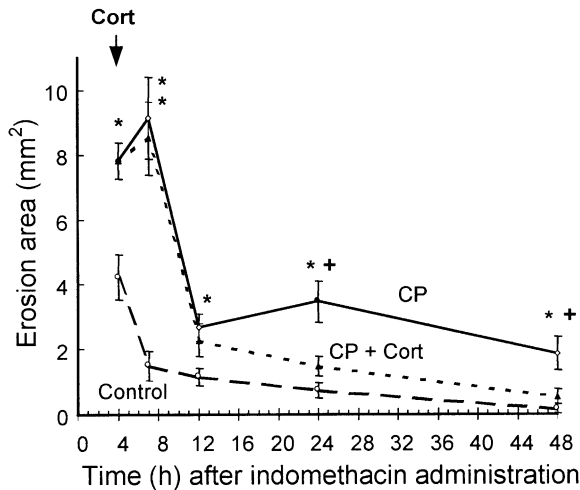


Fig. 6. Effect of corticosterone deficiency followed by injecting corticosterone on the healing of gastric erosions caused by indomethacin injected sc at a dose 25 mg/kg. Corticosterone deficiency was produced by cortisol (300 mg/kg, ip) one week before indomethacin. Replacing corticosterone (4 mg/kg, sc) was injected 4 h after indomethacin administration. Control: saline pretreated group; CP: cortisol pretreated group; CP + Cort: group with cortisol pretreatment followed by a single replacing dose of corticosterone. Animals were killed 4, 7, 12, 24 and 48 h after indomethacin administration. Values are mean  $\pm$  S.E. from 7–12 animals/group. \* $P < 0.05$  compared with Control group, +  $P < 0.05$  compared with CP + Cort group.

in the first 2–3 h were similar to the corticosterone level of control indomethacin treated animals (Fig. 4). This short period of hormonal replacement was enough to induce a positive effect on the healing process in rats with deficiency of glucocorticoid production. Injecting corticosterone significantly improved the healing of indomethacin-induced gastric erosions in both adrenalectomized and cortisol pretreated rats (Figs. 5 and 6). This accelerating effect of the corticosterone first appeared 20 h after its injection (in time point “24 h after indomethacin administration”; Figs. 5 and 6).

#### 4. Discussion

The present results indicate that administration of indomethacin at an ulcerogenic dose induces corticosterone release, which in turn may help protect the gastric mucosa against indomethacin-induced injury. The data obtained show that the loss of indomethacin-induced corticosterone rise potentiates the formation and delays the healing of indomethacin-induced erosions and replacing corticosterone reverses both these effects of glucocorticoid deficiency. According to these results, the endogenous glucocorticoids have gastro-protective actions that could be realized during both the formation and the healing of indomethacin-induced injury.

Two methods for the creation of glucocorticoid deficiency were used in present study: adrenalectomy and

corticosterone pretreatment. Adrenalectomy promoted the ulcerogenic action of indomethacin and an acute corticosterone replacement mimicking indomethacin-induced corticosterone rise in adrenalectomized rats prevented erosion-promoting effect of adrenalectomy.

Adrenalectomy decreases basal corticosterone levels, which may also contribute to protection of gastric mucosa against indomethacin-induced injury. There are conflicting reports concerning the effect of adrenalectomy on the formation of indomethacin-induced gastric erosions. Diahanguiri et al. [4] did not find any effect of adrenalectomy on indomethacin-induced erosions. At the same time, in other investigations [22,25], an aggravating effect of adrenalectomy on indomethacin-induced erosions was found and it has been shown that glucocorticoid deficiency is the reason of the aggravation.

The potentiating influence of adrenalectomy on the formation of gastric erosions caused by indomethacin is in good agreement with our results obtained in the other model where indomethacin-induced glucocorticoid production was inhibited by delayed action after a single high dose of cortisol (300 mg/kg, ip) injected 1 week before indomethacin administration. The result of a previous study [8] showed that the inhibition of HPA axis at all three levels (hypothalamus, pituitary and adrenal) is the reason for a decrease of glucocorticoid production after cortisol pretreatment.

Cortisol pretreatment alone did not cause pathological changes in the stomach. It appears that excess amount of the hormone per se does not have an ulcerogenic effect. However, if indomethacin administration followed the administration of cortisol 1 week later the formation of indomethacin-induced injury was enhanced. Replacing corticosterone again attenuated the effect of glucocorticoid deficiency induced by cortisol on indomethacin-induced gastric erosions.

It is well known that the gastric mucosal injury induced by indomethacin as well as other NSAIDs limits the use of these drugs for the treatment of chronic inflammatory disorders and simultaneous treatment with therapeutic doses of glucocorticoids increases the risk for gastric pathology [12,15,28]. The present data obtained in two models of the hormonal deficiency suggest that indomethacin treatment in patients with deficiency of glucocorticoid production may also be associated with increased risk for gastric side effects. The mechanisms whereby exogenous glucocorticoids at pharmacological doses induce gastric lesions are complex and might involve a suppression of prostaglandin synthesis through an inhibition of phospholipase A2 [1]. In addition, we suggest that in cases of terminating lasting glucocorticoid therapy an increased susceptibility to gastric mucosal injury may be due paradoxically to the suppression of the rapid endogenous glucocorticoid release during the period of erosion formation. This

point is supported by the present data obtained with a pretreatment by pharmacological dose of cortisol. In contrast to the action of pharmacological doses of glucocorticoids, the effect of physiological dose of administered glucocorticoids may be gastroprotective, as shown by the present results with indomethacin as well as obtained with stress [7,8,10,11].

The present results corroborate our previous data demonstrating a gastroprotective role of glucocorticoids during stress action [5–8]. According to the results obtained in our investigations the glucocorticoid rise is an important defensive factor maintaining mucosal integrity during action of stress or indomethacin exposure. Therefore, gastric protective mechanisms triggered by the brain may involve an activation of HPA axis.

In accordance with the present data, endogenous glucocorticoids could serve not only to protect against the formation of indomethacin-induced gastric erosions but also to aid in the healing previously formed injury caused by indomethacin.

The association between therapeutic doses of glucocorticoids and delay in gastric ulcer healing is not controversial. The data of literature concern the lasting glucocorticoid therapy or the effects of exogenous glucocorticoids injected at pharmacological doses on healing of gastric mucosal injury and show that these hormonal actions delay the natural healing of experimental gastric injury [3,13,14,16].

In the present study, we evaluated the physiological role of glucocorticoids. Our results show that in rats with deficiency of glucocorticoid production the healing processes are slower compared with those in animals having normal glucocorticoid production. Injected corticosterone significantly improved the healing of indomethacin-induced injury in rats with deficient glucocorticoid supply. So, on the base of our data obtained in two models of deficient glucocorticoid production followed by corticosterone replacement we can suggest that a natural glucocorticoid production helps in the recovery of gastric mucosal integrity after indomethacin action. Thus, the gastroprotective role of glucocorticoids is also supported by the beneficial effect of glucocorticoids on the healing of indomethacin-induced erosions.

There is general agreement that the main mechanism whereby indomethacin induces gastric erosions is through its ability to inhibit cyclooxygenase-mediated production of prostaglandins [17,26,29], which has an important role in maintaining the integrity of gastric mucosa [19,21]. In addition, indomethacin-mediated gastric injury may involve many other factors—alone or in combination—such as gastric hypermotility, impaired microcirculation, neutrophil–endothelial cell interaction and superoxide radicals. At present there are two major hypotheses for the critical pathogenic factor in gastric injury induced by indomethacin: the motility hypothesis [23,24] and neutrophil hypothesis [18,27]. We speculate

that endogenous glucocorticoids may decrease the ulcerogenic action of indomethacin due to either an improvement of gastric mucosal state through maintenance of local gastric defensive factors and/or through attenuation of local aggressive factors, for example such as a motility induced by indomethacin [22].

The importance of the glucocorticoids for bodily defences during the stress syndrome has been reaffirmed recently by Sapolsky et al. [20]. The normal basal production of glucocorticoids is important for the gastric mucosa to resist indomethacin challenge [22] and this mode of action might be classified as a permissive glucocorticoid action. Administration of indomethacin triggers an adrenocortical response. In our experiments, the acute elevation of the native glucocorticoids in the physiological range during indomethacin action as well as stress [7] may itself be gastroprotective in connection with the formation of indomethacin- or stress-induced erosions. This corticosterone response can be regarded as an active defence by the HPA axis (a “stimulatory” glucocorticoid action) helping the organism to survive the challenge posed by the stressful event(s). Glucocorticoid replacement has a beneficial role even after erosion formation, during the period of healing of the gastric damage induced by indomethacin. Although our data are consistent with both a permissive and a “stimulatory” corticosterone effect on improving erosion healing, we speculate that the effects on healing are more likely to include a permissive rather than “stimulatory” corticosterone action on gastric mucosa.

In summary, the present data demonstrate that the reduction of indomethacin-induced corticosterone release promotes the formation and delays the healing of indomethacin-induced gastric erosions in rats. Injecting corticosterone significantly decreases the formation of indomethacin-induced gastric erosions in rats with glucocorticoid deficiency and promotes their healing. Thus, the present study suggest a physiological gastroprotective action of glucocorticoids in the formation and in the healing of indomethacin-induced mucosal injury.

## Acknowledgements

We would like to express our sincere appreciation to Dr. Anatoly Bogdanov for technical assistance. This study was supported by grants from the Russian Foundation of Fundamental Investigations (RFFI N 96-15-97793 and RFFI N 98-04-48425) and from the St. Petersburg Scientific Center of the Russian Academy of Sciences (2000-N 36).

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