Corticosterone increase inhibits stress-induced gastric erosions in rats

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Filaretova, L. P., A. A. Filaretov, and G. B. Makara. Corticosterone increase inhibits stress-induced gastric erosions in rats. Am. J. Physiol. 274 (Gastrointest. Liver Physiol. 37): G1024–G1030, 1998.—The role of glucocorticoids released in response to stress in the pathogenesis of stress-induced gastric erosions has been reevaluated. Gastric erosions elicited in male rats by 3-h cold-restraint or water-restraint stresses were studied after acute reduction of corticosterone release or occupation of glucocorticoid receptors by the antagonist RU-38486 during stress. Stress-induced corticosterone production was reduced by creating a lesion on the hypothalamic paraventricular nucleus (PVN) 4 days before stress as well as by pretreatment with a rabbit antiserum to adrenocorticotropic hormone (ACTH) 30 min before stress. RU-38486 (10 mg/kg po) was administered 20 min before and 60 min after the onset of stress. Corticosterone for replacement was injected 15 min before the onset of stress to mimic stress-induced corticosterone response. Plasma corticosterone levels were measured by fluorometry or RIA. Gastric erosions were quantitated by measuring the area of damage. Four days after PVN lesion, stress-induced corticosterone release was decreased and gastric erosions were increased. Injecting corticosterone significantly attenuated the effect of PVN lesion on gastric erosions. The ACTH antiserum inhibited corticosterone secretion in response to stress and markedly increased gastric erosions. The administration of the glucocorticoid/progesterone antagonist RU-38486 significantly potentiated the formation of stress-induced gastric erosions. These observations support the suggestion that glucocorticoids released during stress have a gastroprotective action rather than an ulcerogenic effect as was generally accepted.

Gastric erosion; glucocorticoids; hypothalamic lesion; RU-38486

Corticosteroids and gastric ulceration have been discussed in many contexts. Various types of gastric damage (acute stress erosions vs. peptic ulcer disease) and situations with altered glucocorticoid hormone supply (acute and chronic stress-induced secretion, acute and chronic treatment of patients or experimental animals with synthetic compounds) have been considered. At present, there is no consensus about the role of the endogenous glucocorticoid hormones in the vulnerability of the stomach.

Numerous studies have shown that in humans (13, 38, 47) and animals (5, 6) high doses of glucocorticoids increase the incidence of gastric ulcers. Based on the notion that exogenous corticosteroids have ulcerogenic properties, the increase of corticosteroids during stress was also considered to be an ulcerogenic factor (31, 46). Despite some studies that failed to support an ulcerogenic action of endogenous glucocorticoids (17, 30, 34, 39), for many years it has been generally accepted that corticosteroids are ulcerogenic hormones, a notion that is difficult to reconcile with the adaptive role of hypothalamic-pituitary-adrenocortical system hormones, as suggested by Munck et al. (28).

A few years ago, the role of endogenous glucocorticoids in stress-induced gastric erosion was reevaluated (8, 9, 11, 12). The hypothesis was that increased susceptibility to experimental erosions after administration of pharmacological doses of glucocorticoids could paradoxically be due to suppression of the acute endogenous corticosteroid release during the period of erosion formation. It was demonstrated that pretreatment with glucocorticoids caused a long-lasting decrease in stress-induced corticosterone release and increased ulcerogenic action in different models of stress (9). It was also demonstrated that acute corticosteroid replacement mimicking stress-induced corticosterone response reduced gastric erosions in rats with blocked hypothalamic-pituitary-adrenocortical systems (11). These studies suggest a gastroprotective role of endogenous corticosteroids released during stress. A gastroprotective role of stress-released glucocorticoids was also demonstrated in our experiments with intrahypothalamic implantation of dexamethasone (11), which blocked the stress-induced corticosteroid response and markedly increased gastric erosions. Replacing corticosterone attenuated the potentiating effect of hypothalamic dexamethasone on stress-induced erosion formation. Therefore our previous investigations (8–11) demonstrated that the deficiency of glucocorticoid production during stress promotes stress-induced gastric erosions in rats and suggests that endogenous corticosteroids have a gastroprotective role under specific conditions.

The present study was performed to further investigate the role of stress-induced corticosteroid release in stress-induced gastric erosions using short-lasting and smaller changes in glucocorticoid supply. Stress-induced glucocorticoid production was reduced by 1) creating a lesion on the hypothalamic paraventricular nucleus (PVN) 4 days before stress and by 2) pretreatment with an antiserum to adrenocorticotropic hormone (ACTH) 30 min before stress. In addition, the glucocorticoid/progesterone-receptor antagonist RU-38486 was used to interfere with the actions of corticosteroids released during stress.
MATERIALS AND METHODS

Experiments were performed in St. Petersburg or Budapest. Similar methods were used in the two laboratories, although differences in hormone measurement methods as well as in rat strain remained. Care was taken to ensure that experiments produced similar results in the two laboratories and that interlaboratory differences did not influence the conclusions drawn within the experiments. However, the extent of ulcer lesion cannot be compared between different experiments since pretreatment of the control rats varied according to the purpose of the experiment and laboratory conditions were similar but not identical. The institutional animal care committee approved the experimental protocols in Budapest.

Animals and Experimental Procedure

Adult male Wistar rats weighing ~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 ± 1°C, free access to food and water) for 5–7 days before use. In all experiments the animals were deprived of food but not water for 24 h before initiation of the restraint procedure and grid floors were placed in the home cages to prevent coprophagy.

Stress Stimulus

Rats were restrained for 3 h either in a cold room (temperature 4°C) or in water (temperature 18°C) as specified in RESULTS. The rats were restrained on a board, as described previously by Renaud (36). At the end of the 3-h stress exposure, the animals were killed by decapitation and stomachs were removed for measuring the areas of erosion.

Blood Sampling

Blood was collected before and during stress (at 15, 30, 60, and 180 min after the onset of stress) through an indwelling venous cannula placed 1 day earlier. Blood samples (0.3 ml) were replaced by an identical volume of physiological saline. The samples were centrifuged at 4°C, and the plasma was frozen for hormone analysis.

Surgical Methods

All rats were surgically manipulated under pentobarbital anesthesia (40 mg/kg i.p. Nembutal; Serva, Heidelberg, Germany). The bilateral PVN lesion was made with a triangular rotating knife (24). To create the lesion, rats were mounted in a stereotaxic apparatus with the nose down by an angle of 11°. The knife was lowered into the brain at 1.8 mm behind the bregma in the midline through the sagittal sinus until the tip touched the base of the skull. The lesion was then made by turning the knife 360° to the left and 360° to the right. For sham lesion, the knife was lowered into the brain and not turned at all.

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.

Experiment 1: effect of PVN lesion on stress-induced gastric erosions. Three days after the PVN or sham lesions were performed, a chronic venous cannula was implanted. One day later the exposure to stress occurred. After collection of the basal blood samples, PVN- or sham-lesioned rats were stressed (3 h of cold-restraint or 3 h of water-restraint stress). Five blood samples were collected during stress in each rat.

First, the gastric erosions as well as the corticosterone response to cold-restraint stress were compared between PVN- and sham-lesioned rats. Second, the gastric erosions as well as the corticosterone response to water-restraint stress were compared in rats with 1) sham operation, 2) PVN lesion, or 3) PVN lesion with replacement of corticosterone before stress. The corticosterone replacement consisted of injecting corticosterone (4 mg/kg in 1 ml/kg 1,2-propylene glycol sc; Serva) 15 min before stress in rats with PVN lesion. The rats without corticosterone replacement were injected with the same volume of vehicle at the same time.

Three hours after the onset of stress, the rats were decapitated, the brains were fixed in 10% formaldehyde, and the hypothalamus was embedded in paraffin and sectioned in the coronal plane. Every fifth 10-µm section was mounted and stained with the crotonaldehyde-fuchs in method with carminic acid as a counterstain. For analysis we retained only data derived from rats with complete bilateral PVN lesion.

Experiment 2: effect of ACTH antiserum on stress-induced gastric erosions. Rabbit antiserum to ACTH at a dose of 1 ml/rat was injected via the chronic venous cannula 30 min before the onset of stress. Control rats received normal rabbit serum in a volume of 1 ml/rat at the same time. The ACTH antiserum (RU-38486) was raised in two rabbits (nos. 7,702 and 7,703) and directed against the midportion of the ACTH (1–39) molecule, as it did not crossreact with α-melanocyte-stimulating hormone or COOH-terminal peptides. Fifty percent binding of a trace amount of 125I-ACTH was tested in an RIA system (1,470,000 vs. 1,220,000 for no. 7,702 vs. 7,703, respectively). The lyophilized ACTH antiserum was dissolved just before injection. ACTH antiserum or normal rabbit serum was injected immediately after collection of the basal blood sample. Thirty minutes after injection the animals were restrained in the cold. Blood samples were collected during stress through an indwelling cannula. In a preliminary experiment, it was established that 1 ml of the ACTH antiserum abolished the corticosterone response to a mild stress, while 0.5 ml was only partially effective.

Experiment 3: effect of RU-38486 on stress-induced gastric erosions. The glucocorticoid/progesterone-receptor antagonist RU-38486 (11b,17b)-11-[4-(dimethylamino)-phenyl]-17-hydroxy-17-(1-propyny1) estr-4,9-dien-3-one; Roussel-Uclaf, Paris, France) was administered twice orally in a dose of 10 mg/kg, first 20 min before and then 60 min after the beginning of the 3-h water-restraint stress exposure. RU-38486 was prepared as a suspension in a vehicle containing 1% methylcellulose and 0.05% Tween 80. Control rats received the vehicle orally (2.5 ml/kg) at the same time. An additional control group of animals restrained without administration of vehicle was also used, and plasma corticosterone level was not measured in this experiment.

Estimation of Gastric Erosions

After the rats were killed, the stomachs were removed and filled with 10 ml of 1% Formalin. Thirty minutes later, each stomach was opened by cutting along the greater curvature, cleaned, and spread. The stomach was examined with a special television system permitting measurement of the area of lesion (12), or with a binocular dissection microscope. Color photographs of the mucosal surface were taken as a record of the erosions. 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. Although the lesions were acute hemorrhagic gastric erosions, they are commonly referred to as “stress ulcers” (18).

Hormone Measurements

The corticosterone level of plasma was measured by either microfluorometry (4) or RIA (26). Intra- and interassay varia-
tion of the measurements was 5.1% and 7.4%, respectively, for the fluorometric assay and 6.4% and 15.3%, respectively, for the RIA.

Statistical Analysis

Data are means ± SE. We used the nonparametric Kruskal-Wallis test followed by the 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.

RESULTS

The cold-restraint or the water-restraint procedure produced typical gastric lesions in each experiment, with an area of damage in the controls ranging from 0.2 to 2.9 mm² in the various series. This variation in the size of lesions is probably due to the sham procedures applied to the various control groups, including methylcellulose vehicle (known to coat the mucosa) and surgery for venous cannula implantation with or without sham PVN lesion before the acute ulcerogenic stress procedure. Preliminary studies have shown that the 3-h sampling procedure did not change plasma corticosterone levels in sham-operated or PVN-lesioned rats. During the 180 min of sampling, plasma levels were 9.7 ± 1.9, 16.3 ± 2.3, 13.3 ± 2.1, 13.4 ± 3.8, 13.7 ± 3.4, and 9.6 ± 2.4 µg/dl at 0, 15, 30, 60, 120, and 180 min, respectively.

The lesions placed with the rotating wire knife destroyed an inverted cone of hypothalamic tissue centered on the PVN. The size and the histology of the lesion were similar to those described previously (24) and eliminated all neurosecretory cells within the PVN (Fig. 1). Four days after PVN lesion there was no difference between baseline corticosterone levels in PVN-lesioned and sham-lesioned rats (Fig. 2A). The cold-restraint-induced corticosterone levels were significantly lower in the PVN-lesioned rats than in the sham-operated animals at all time points from 30 to 180 min of stress. Although corticosterone levels in the PVN-lesioned, stressed rats were significantly lower than in the controls, they were also significantly above the prestress hormone levels at all time points during stress. Erosions were not observed in any unstressed rats regardless of pretreatment. Cold-restraint stress induced gastric erosions both in PVN-lesioned and sham-operated rats. The area of erosion in PVN-lesioned rats was considerably larger than that in control animals (Fig. 2B). Thus PVN lesion induced a decrease in stress-induced corticosterone response and an increase in stress-induced gastric erosions.

In another experiment, the corticosterone levels in response to water-restraint stress were significantly lower in the PVN-lesioned rats than in the sham-operated rats (P < 0.05) at all time points from 30 to 180 min of stress (Fig. 3A). Corticosterone injected in a
dose of 4 mg/kg before water-restraint stress overcompensated for the reduction of stress-induced glucocorticoid production in PVN-lesioned rats (Fig. 3A). There was no difference between baseline corticosterone levels in all investigated groups (Fig. 3A). Water-restraint stress induced gastric erosions in all investigated groups; however, the extent of the damage differed (Fig. 3B). The PVN lesion again potentiated stress-induced gastric erosions. The average area of stress-induced erosions in PVN-lesioned rats was much larger than that in the sham-operated rats. Replacing corticosterone prevented the erosion-promoting effect of PVN lesion (Fig. 3B). After corticosterone replacement the average area of gastric erosions in PVN-lesioned rats did not differ from that in control sham-operated rats (P > 0.9).

Administration of an ACTH antiserum at a dose of 1 ml/rat 30 min before the onset of cold-restraint stress resulted in a marked decrease of corticosterone response to this stress. After administration of ACTH antiserum, the stress-induced corticosterone levels were about one-third of that in the control rats pretreated with normal rabbit serum (Fig. 4A). We observed these differences at all time points up to 180 min of stress (P < 0.01). Stress-induced corticosterone levels in ACTH antiserum-treated rats, although quite low, were significantly higher than basal corticosterone levels during the first 120 min of stress but did not differ from the basal levels at 180 min of stress (Fig. 4A). Acute treatment with ACTH antiserum (1 ml/rat) significantly potentiated the ulcerogenic effect of stress. The area of gastric erosions caused by stress was significantly larger in rats treated with the antiserum than in the control group (Fig. 4B).

The oral administration of RU-38486 in two doses of 10 mg/kg each before and during stress significantly potentiated the formation of stress-induced gastric erosions. The average area of 3-h water-restraint-induced gastric erosions in rats treated with RU-38486 was markedly larger than that in control animals, which received vehicle alone (Fig. 5). Comparison of the results of two control groups showed that the methylcellulose vehicle given orally to fasted rats before and during stress in itself decreased the area of the stress-induced erosions [erosion area was 2.89 ± 0.95 and 0.19 ± 0.05 mm² for untreated controls (n = 11) vs. methylcellulose-treated rats (n = 10), respectively].

**Discussion**

The present findings show that a decrease of the acute corticosterone increase or a blockade of glucocorticoid receptors during stress enhances the vulnerability of the stomach during cold-restraint and water-restraint stressors. According to these results, an acute increase in corticosterone seems to protect the gastric mucosa against stress-induced erosions.

By creating a lesion on the PVN, we were able to reduce the acute glucocorticoid response so that neither the lasting effects of previous glucocorticoid treatment (9) nor the hypothalamic side effect of glucocorticoid implants (11) had a confounding action on the results. By making a lesion on the PVN, we removed the main source of corticotropin-releasing hormone (CRH)-producing neurons projecting to the median eminence and decreased stress-induced corticosterone response, consistent with previous findings (7, 24). The decrease in stress-induced corticosterone release was associated with an increase in gastric erosion, induced either by cold-restraint or water-restraint stress. The potentiating influence of PVN lesion on gastric erosions induced by water-restraint stress is in agreement with a study by Aou et al. (2) demonstrating the increase in water-restraint-induced gastric damage after electrolytic PVN lesion. There is evidence that the PVN markedly influences the autonomic regulation of gastric function (37) and may influence erosion formation through changes involving autonomic regulation of gastric secretion. However, the experiment with PVN lesion and corticosterone replacement (Fig. 3) supports a significant role of the adrenocortical hormone in gastroprotection.

Thus PVN lesion (present study) as well as cortisol pretreatment or dexamethasone implantation (9, 11) resulted in a decrease in corticosterone response to...
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Experiments with replacing corticosterone suggest that stress and a concomitant increase in gastric erosions. The main factor in the increase in gastric erosions in all of these cases was the reduced corticosterone response to stress. It should be noted that in the PVN-lesioned rats both stressful procedures (water-restraint or cold-restraint stress) elicited appreciable increases in plasma corticosterone, despite the fact that the site of origin of the CRH-containing fibers projecting to the median eminence was destroyed. Although most studies with PVN lesion describe a residual stress-induced elevation of plasma corticosterone (see Refs. 7 and 24), it is generally not appreciated that the increases obtained with strong stimuli may reach about one-half of the usual corticosterone elevation. It is not known whether the few CRH-containing neurons outside the PVN, which may project to the median eminence after PVN lesions, mediate the substantial corticosterone elevations (24, 33) also observed in the present studies or whether an as yet unidentified hypothalamic mediator (maybe urocortin; Ref. 45) plays a role when CRH of PVN origin is absent.

Further support for a gastroprotective role of corticosteroids released during stress in the stress-induced erosions comes from the studies using an ACTH antiserum. In this case a short-lasting corticosterone reduction was produced by immunoneutralization of plasma ACTH. The administration of the ACTH antiserum 30 min before stress reduced the fast corticosterone response to cold-restraint stress and enhanced the stress-induced gastric erosions. Data with ACTH antiserum give strong support for the idea that stress-induced gastric erosions are potentiated by a reduction of glucocorticoid production during stress.

Glucocorticoid antagonists offer another way to evaluate the role of the stress-induced corticosterone increase in gastric erosions. The specific progesterone/glucocorticoid receptor antagonist RU-38486 is known to bind with a high affinity to type II but not to type I glucocorticoid receptors (27, 43) and may influence peripheral as well as central glucocorticoid receptors. In the simultaneous presence of the glucocorticoids and the antagonist in vivo, glucocorticoid receptors are preferentially occupied by the antagonist (1). The RU-3846-glucocorticoid receptor complex is incapable of nuclear translocation and does not produce a biological effect (27). Administration of RU-3846 caused a significant increase in the incidence of stress-induced erosions: the gastric damage evoked by 3-h water-restraint stress in RU-3846-treated rats was considerably higher than that observed in control (vehicle-treated) animals. It is difficult to estimate the degree of in vivo occupation of glucocorticoid receptors caused by RU-3846 treatment. However, the dose (10 mg/kg twice) and the timing and route of administration (oral) of the antagonist probably maximized occupation of glucocorticoid receptors during stress.

We consider our results with RU-3846 administration to further support the gastroprotective role of glucocorticoids released during stress. The glucocorticoid antagonist RU-38486 was also shown to potentiate aspirin-induced gastric damage and to reduce the gastroprotective efficacy of interleukin-1 (34).

The role of endogenous glucocorticoids in stress-induced gastric erosions has been debated. Weiss (46) found that the degree of ulceration after stress correlated positively with the level of plasma corticosterone. On the basis of these results as well as data about the ulcerogenic properties of exogenous corticosteroids, Weiss proposed that “steroids, in quantities that the animal is capable of secreting, may contribute to the production of ulcers” (46). Further support for this notion came from the observation that animals with hippocampal lesions exhibit increased plasma corticosterone levels and develop more gastric erosions during stress (31). Thus, on the basis of these studies, the corticosterone increase during stress was considered to be an ulcerogenic factor. However, opposing findings have also been reported; a significant negative correlation was found between adrenocortical activity and the degree of stress-induced gastric erosions (29). Moreover, Murison et al. (30) have observed that metyrapone treatment, which slightly reduced corticosterone levels under stress, had no effect on erosions and concluded that the findings do not support a simple causal relationship between adrenocortical activity and gastric ulceration. Recently, corticosterone secretion during stress has been considered to be a correlational phenomenon rather than a causal factor in gastric pathology (3). In contrast, based on our previous (8–11) and present findings we suggest that an acute increase of corticosterone during stress is a potent gastroprotective component of the hormonal response to stress.

We propose that the corticosterone increase during stress protects from gastric erosions if the level of corticosterone reaches near-maximal stress-induced levels. It should be noted that each of our models induced at least 50% inhibition of corticosterone increase, as indicated by the area under the curve. The absence of effect on erosions after metyrapone treatment (30) may be explained by the putative gastroprotective effect of cortolone secreted in large quantities after metyrapone treatment and by the fact that inhibition of corticosterone increase by metyrapone is insufficient to interfere with gastric erosions. Additional studies are needed to elucidate whether graded changes of plasma corticosterone during stress would result in a graded gastroprotective effect.

Adrenalectomy has frequently been used for studying the role of corticosteroids in gastric erosions, with conflicting results. Most studies have shown that adrenalectomy potentiates gastric erosions (34, 39, 42). However, there have also been reports that adrenalectomy does not influence erosions (25) or decreases them (22, 35). In addition, the effect of adrenalectomy may depend on the kind of stress. Moreover, it was shown that even using the same kind of stress, the effect of adrenalectomy can be completely different in rats of different strains (35). One reason for the inconsistent effects of adrenalectomy may be the removal of adrenomedullary catecholamines. It is well known that cate-
cholamines can provoke acute gastric lesions in different experimental animals (32, 44), and adrenal medullectomy alone significantly diminished ethanol-induced gastric mucosal damage (39). To estimate the role of the glucocorticoids released during stress in gastric erosions, we reduced acute glucocorticoid secretion by various methods not interfering with adrenomedullary catecholamines, and the deficiency elicited by these methods promoted gastric erosions.

In most of our experiments there might be changes in hypothalamic CRH. Cortisol pretreatment changed the usual hypothalamic CRH response to cold-restraint stress (11). Dexamethasone implantation in PVN resulted in a local decrease in corticotropin-releasing factor (CRF) mRNA (21) and prevented the increase of CRF immunostaining induced by adrenalec- tomy (20). PVN lesion removed hypophysiotropic CRH-producing neurons. In all these cases prominent changes are expected in the contents of CRH related to the hypothalamic-pituitary-adrenocortical system in the median eminence or in the PVN, but we could not exclude the possible changes in content of CRH elsewhere in the brain, possibly related to effects on the gastric mucosa. It is known that CRH as a mediator in the nervous system improves gastric defense mechanisms and protects against gastric erosions (14, 23, 40). However, because acute corticosterone replacement reduced stress-induced erosion formation in all of our rats where it was tested [cortisol pretreatment, dexametha- sone implantation (Refs. 9–12), and PVN lesion], we suggest that in our experiments the major potentiating factor in gastric erosions was corticosteroid reduction rather than CRH inhibition at the hypothalamic level.

Our data show that corticosteroids released during stress protect the gastric mucosa against stress-induced damage: gastric erosions increase when corticosterone secretion is inhibited or glucocorticoid receptors are occupied by an antagonist. In addition, replacement in our experiments or glucocorticoid pretreatment in studies by Hernandez et al. (17) and Hernandez and Glavin (18) reduced stress-induced gastric erosions.

Glucocorticoids may have a permissive role in allowing gastroprotective mechanisms to exert their full potential. A permissive role was suggested in gastric mucosal protection induced by prostaglandins, sulphydryls, cimetidine (39), or interleukin-1 (34). An acute elevation of glucocorticoids during stress may itself be gastroprotective in connection with stress erosions.

It should be emphasized that the effects of glucocorticoids in the physiological range may be different from those of pharmacological amounts, and the glucocorticoid action may be biphasic. The gastroprotective action may also depend on the nature of the damaging agent, as we have evidence that RU-38486 (two doses of 10 mg/kg, po) does not influence the gastric damage caused by 60% ethanol within 2 h or intraperitoneal injection of aspirin within 3 h (Filaretova and Makara, unpublished data).

The gastroprotective action of glucocorticoids released during stress may involve changes in gastric microcirculation (10), a dominant gastroprotective factor (15). Using in vivo microscopy for the direct visualization of gastric microcirculation (19), we investigated the effects of the deficiency of stress-induced glucocorticoid production as well as corticosterone replacement on gastric microcirculation in rats anesthetized after ulcerogenic stress. The deficiency of glucocorticoid production during water-restraint stress promoted the stress-induced decrease of blood flow velocity in submucosal and mucosal microvessels, and corticosterone replacement eliminated this effect (10). These data suggest that the gastroprotective action of glucocorticoids during stress may be provided by the maintenance of gastric blood flow.

The present experiments were designed to test the participation of corticosterone in gastroprotection during acute stress, and the three approaches (PVN lesion with replacement, ACTH immunoneutralization, and glucocorticoid antagonist administration) taken together strongly argue for a role of endogenous glucocorticoids in gastroprotection. We regard this action of the glucocorticoids as an additional factor, and the present findings do not modify in any way the knowledge already available on the role of the PVN in autonomic control of the stomach, the role of central CRH in gastroprotection, the role of vagal outflow and medullary TRH pathways in the pathogenesis of cold-restraint-induced gastric lesions (16, 41, 48), or the role of well-known local gastric cytoprotective mechanisms.

In summary, the present studies suggest that the reduction of stress-induced corticosterone release, or its actions, promotes stress-induced gastric erosions in rats. We conclude that an acute stress-induced increase of corticosteroids has a gastroprotective action against stress-induced gastric damage.

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