Role of Gastric Microcirculation in the Gastroprotection by Glucocorticoids Released During Water-Restraint Stress in Rats

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Abstract

Our previous investigations demonstrated that glucocorticoids released in response to stress protect gastric mucosa against stress-induced ulceration. This study was designed to determine whether gastric microcirculation is involved in the mechanism of gastroprotective glucocorticoid action. For this we evaluated the effects of deficiency of glucocorticoid production during 3 hr water-restraint stress and corticosterone replacement on the stress-induced gastric erosions, gastric microcirculation and arterial pressure in rats. The stress was produced in awake rats and gastric microcirculation and arterial pressure were evaluated in animals anesthetized in 3 hr after the onset of water-restraint stress. An in vivo microscopy technique for the direct visualization of gastric microcirculation was employed. The gastric submucosal and the superficial mucosal microvessels were monitored on television screen through a microscope and the pictures were stored by microfilming for the analysis of red blood cell velocity and vessel diameter. Gastric microcirculation was estimated on the base of both the volume blood flow velocity in submucosal microvessels and the diameter of superficial mucosal venous microvessels. Gastric erosions were quantitated by measuring the area of damage. Plasma corticosterone levels were also measured after 3 hr stress by fluorometry. Water-restraint stress induced an increase in corticosterone level, an appearance of gastric erosions, a decrease in volume blood flow velocity of submucosal microvessels, a dilatation of superficial mucosal microvessels, a decrease in arterial pressure. The deficiency of glucocorticoid production during water-restraint stress promoted the stress-induced gastric ulceration, a dilatation of mucosal microvessels, a decrease of blood flow velocity in submucosal microvessels and of arterial pressure. Corticosterone replacement eliminated the effects of deficiency of glucocorticoid production on all of the parameters under study. Thus, the stress-induced corticosterone rise decreased gastric ulceration, restricted both the reduction of blood flow velocity in submucosal microvessels and a dilatation of superficial mucosal venous microvessels during water-restraint stress. These data suggest that the gastroprotective action of glucocorticoids during stress may be provided by the maintenance of gastric blood flow.

Key Words: gastric erosion, gastric microcirculation, glucocorticoids, stress

Introduction

According to the traditional view based on the notion about ulcerogenic properties of exogenous corticosteroids (2, 3, 22, 27) an increase in glucocorticoid release during stress is an ulcerogenic factor (18, 26). Our previous studies suggested an opposite view. In accordance with our point of view and results obtained the acute rise of glucocorticoid production during stress is gastroprotective factor (5, 6, 7, 9). The role of endogenous glucocorticoids in stress-induced gastric ulceration was reevaluated in our investigations by the different approaches creating the reduction of stress-induced corticosterone release

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or the occupation of glucocorticoid receptors during stress in rats. It was demonstrated that the deficiency of stress-induced glucocorticoid production caused by the pretreatment with cortisol at pharmacological doses or the intrahypothalamic implantation of dexamethasone one week before stress as well as the immunoneutralization of plasma adrenocorticotrophic hormone or the hypothalamic paraventricular nucleus (PVN) lesion markedly potentiated a gastric erosion formation (6, 7, 9). An acute corticosterone replacement mimicking stress-induced corticosterone response significantly attenuated the potentiating effect of cortisol or dexamethasone pretreatment as well as PVN lesion on stress-induced ulceration. The occupation of glucocorticoid receptors by RU-38486 also resulted in an increase in gastric erosion formation during stress. Thus, these observations support the suggestion that glucocorticoids released during stress have a gastroprotective action against stress-induced gastric damage.

This study was undertaken to elucidate the possible mechanisms of gastroprotective glucocorticoid action. In spite of a general acceptance that the cause of gastric ulceration is an imbalance between aggressive and defensive factors, in the last years, however, greater attention has been paid to the defensive factors and especially to the vascular factor (11, 12, 13, 14). It is well established that impaired gastric blood flow may result in decreased mucosal resistance to H^+, bile salt and other barrier breakers (12). The mucosal ischemia occurring under stress conditions represents one of the main factors leading to stress ulceration. It was shown when stress-induced ulceration did occur, the area of the lesion involved a hyperemic region of the mucosa adjacent to the lumen (12). The decrease in submucosal and mucosal blood flow during stress as well as the engorgement of the mucosa in the result of mucosal vein constriction are an important factors leading to a mucosal ischemia, an impairment in tissue resistance and permitting subsequent ulceration by peptic acid secretion in stressed animals (12, 21, 23).

Utilizing an in vivo microscopy technique for the direct visualization of the gastric microcirculation as well as methods creating the alterations in glucocorticoid supply, the present study was designed to determine whether gastric microcirculation is involved in the mechanism of gastroprotective glucocorticoid action during stress.

Materials and Methods

Animals and Experimental Procedure

Adult male Sprague Dawley rats weighing about 250 g were used. Animals were housed five per cage and acclimatized to standard laboratory conditions (lights on between 08.00 and 20.00, temperature 20±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 hours before initiation of the restraint procedure and grid floors were placed in the home cages to prevent coprophagy.

To determine whether the gastroprotective action of glucocorticoids released during stress may involve changes in gastric microcirculation the effect of deficiency of glucocorticoid production followed by corticosterone replacement on stress-induced gastric microcirculation as well as on gastric erosions and systemic arterial pressure were investigated.

Both the blood flow velocity in submucosal microvessels and the diameter of superficial mucosal venous microvessels were used for the estimation of gastric microcirculation.

We estimated and compared the parameters of gastric microcirculation as well as gastric erosion and systemic arterial pressure in rats: 1) unstressed, with normal glucocorticoid production; 2) stressed, with normal glucocorticoid production; 3) stressed, with deficiency of glucocorticoid production; 4) stressed, with deficiency of glucocorticoid production followed by corticosterone replacement.

Stress Stimulus

Rats were restrained in a clear plastic perforated tube for 3 h in water (temperature 18 °C). At the end of the 3-h stress exposure one half of stressed animals were killed by decapitation for the estimation of corticosterone level and gastric erosions and another half of rats were anesthetized with pentobarbital (Nembutal, SERVA, Heidelberg, Germany; 40 mg/kg i.p.) for the investigation of gastric microcirculation and systemic arterial pressure.

Inhibition of Glucocorticoid Production and Corticosterone Replacement

To inhibit a glucocorticoid release during stress a high dose of cortisol (300 mg/kg bw, ip; 2.5% suspension, 12 ml/kg) was administered seven days before stress procedure. The timing of cortisol treatment was chosen so that during water-restraint the exogenous hormone has already been eliminated but the corticosterone response to stress was still inhibited. Control rats received saline (12 ml/kg bw, ip) one week before stress.

The corticosterone replacement consisted of injecting corticosterone (Serva, Heidelberg, Germany; 4 mg/kg in 1 ml/kg 1,2-propylene glycol, sc) 15 min before stress to rats with cortisol pretreatment. The rats without replacement were injected with the vehicle

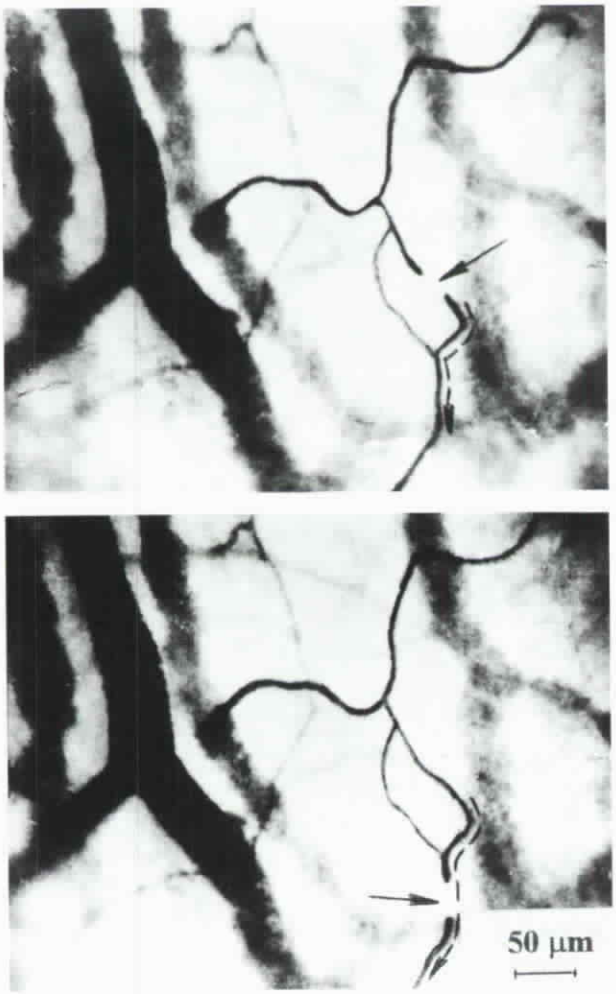

Fig. 1. Photomicrograph showing the shift of the *plasma gap* (arrows) in a stream of erythrocytes in submucosal microvessel. The interval between frames presented is 0.08 s.

in the same volume at the same time.

Estimation of Gastric Microcirculation

The investigation of gastric microcirculation was performed using an in vivo microscopy technique and a cinema-TV complex for the direct visualization and microfilming of microvessels as described previously (17). Briefly, the gastric submucosal and superficial mucosal microvessels were monitored on television screen through a microscope with a dark-field epiobjective and the picture were stored by microfilming for the analysis of red cell velocity and vessel diameter (Fig. 1, 2). The plasma filled "gaps" (spaces filled with plasma) in the continuous erythrocyte flow in microvessels were used as the markers to measure linear red blood cell velocity (Fig. 1). The volume blood flow velocity of submucosal microvessels was calculated from them linear red cell velocity and diameter. The diameters

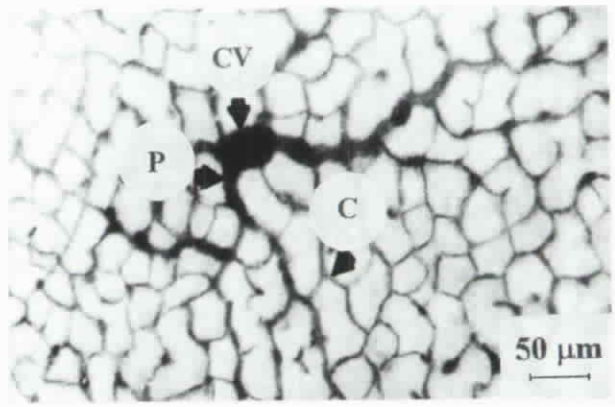

Fig. 2. Photomicrograph showing classification of superficial mucosal microvessels into orders according to their branching hierarchy and relative dimension. C - capillary, P - postcapillary, CV - collecting vein.

of superficial mucosal capillaries, postcapillaries venules and collecting veins were measured (Fig. 2).

For estimation of gastric microcirculation both unstressed and stressed rats were anesthetized, and a midline upper abdominal incision was made. The gastrohepatic ligaments were cut and the stomach exteriorized by gently manipulation. For visualization of the submucosal vascular bed, the serosal and muscle layers were carefully dissected from a small area free of large vessels. The area under study which was continuously bathered with saline at 37 °C was brought into touch with a contact objective. Three fields of vision with some vessels were filmed continually for 20 s in every rats. Immediately after that the stomach was prepared for the estimation of mucosal microvessels. To visualize the superficial mucosa a long incision was made in the anterior wall of the forestomach. The stomach was then everted through the incision, thus exposing the mucosa to direct visualization. The mucosal area under study was also continuously bathered with saline at 37 °C and three fields of vision were filmed in every rats. The systemic arterial blood pressure was also monitored in anesthetized rats via cannula implanted in the left femoral artery.

Estimation of Gastric Erosions

After sacrifice the stomach was removed and filled with 10 ml of 1% formalin. Thirty min later, the stomach was opened by cutting along the greater curvature, cleaned and spread. The stomach was examined with special TV system, allowing to measure the area of lesion (7). 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, the literature commonly refers to this phenomenon as "stress ulcer" (15).

Hormone Measurements

Corticosterone level of plasma was measured by microfluorometry (1). Intra and interassay variation of the measurements were 5.1% and 7.4% for this assay.

Statistical Analysis

The data are presented as means±SE. The nonparametric Mann-Whitney tests was used for comparing erosion scores, parameters of gastric microcirculation, arterial pressure. The differences in corticosterone data were analyzed for statistical significance on the basis the Student t-test or by modification of the Student t-test for population with unequal variances.

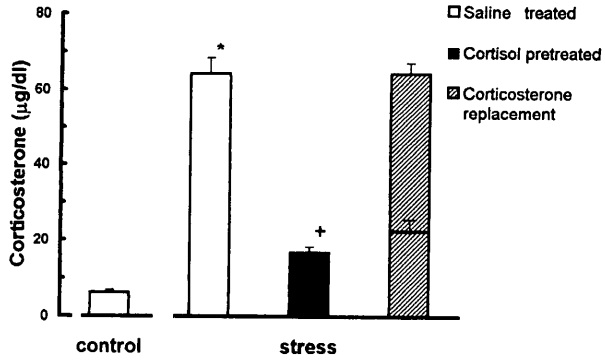

Fig. 3. Effect of cortisol pretreatment (300 mg/kg bw, ip) 7 days before water-restraint stress on the plasma corticosterone level 3 hr after the onset of the stress. Values are means±SE; n=9-35/group. *P <0.05 compared with control; +P<0.05 compared with both the stressed group with saline treated and the group with corticosterone replacement. Corticosterone replacement mimicked the normal corticosterone response to stress during 2 hr after the injection but at 3 hr after one the corticosterone practically disappeared from the plasma. The last column demonstrated corticosterone level in 2 and 3 hr after corticosterone injection.

Results

Glucocorticoid Levels after Cortisol Pretreatment and Corticosterone Replacement

The water-restraint procedure induced a high corticosterone level of plasma in rats untreated by cortisol. Administration of cortisol at dose 300 mg/kg 7 days before water-restraint stress resulted in a marked decrease of corticosterone response to this stress. Stress-induced corticosterone level in cortisol pretreated rats was only about 30% of that in the stressed control rats (Fig. 3). Thus, cortisol at high dose administrated one week before stress caused a deficiency of the stress-induced glucocorticoid production.

Corticosterone injected in a dose of 4 mg/kg 15 min before water-restraint stress compensated for the reduction of stress-induced glucocorticoid production in cortisol-treated rats. Thirty min after corticosterone administration the level of corticosterone in blood (mean±SE) was 102.7±9.4 μg/dl (n=8), 60 min after the administration - 73.5±3.7 μg/dl (n=8). Stress-induced corticosterone level was 91.9±6.5 μg/dl (n=10) 30 min after onset of the water restraint and 77.2±12.9 μg/dl (n=10) 60 min after onset of this stress. Three hours after an injection the corticosterone has practically disappeared from the plasma (Fig. 3).

Effect of the Deficiency of Glucocorticoid Production during Stress on Gastric Ulceration

No pathological changes of gastric mucosa were observed in any unstressed rats from the first to the seven days after cortisol administration. The water-restraint stress produced typical gastric erosion in both rats with normal glucocorticoid production and animals with the deficiency of glucocorticoid production. However, the average area of stress-induced erosions in rats with glucocorticoid deficiency was considerably larger than that in control animals (Fig. 4A). In order to ascertain that the increase in stress-induced gastric ulcer formation is indeed associated with glucocorticoid deficiency, the corticosterone replacement was employed. Replacing corticosterone significantly decreased the stress-induced ulceration in rats with the deficiency of glucocorticoid production (Fig. 4A).

Effect of the Deficiency of Glucocorticoid Production during Stress on Gastric Microcirculation and Arterial Pressure

The blood flow velocity was measured in small submucosal microvessels with mean diameter about 6 μm. There was no significant difference in the diameter of these vessels in the investigated groups. In the same time there were statistically significant alterations in both red blood cell velocity and volume blood flow velocity in submucosal microvessels of all groups under study. The changes of the volume blood velocity were parallel to that of red blood cell velocity.

The results demonstrating the effect of the water-restraint stress on volume blood flow velocity in submucosal microvessels of rats with a different glucocorticoid supply are presented on Fig. 4B. The maximal volume blood flow velocity in submucosal microvessels was discovered in unstressed rats. The

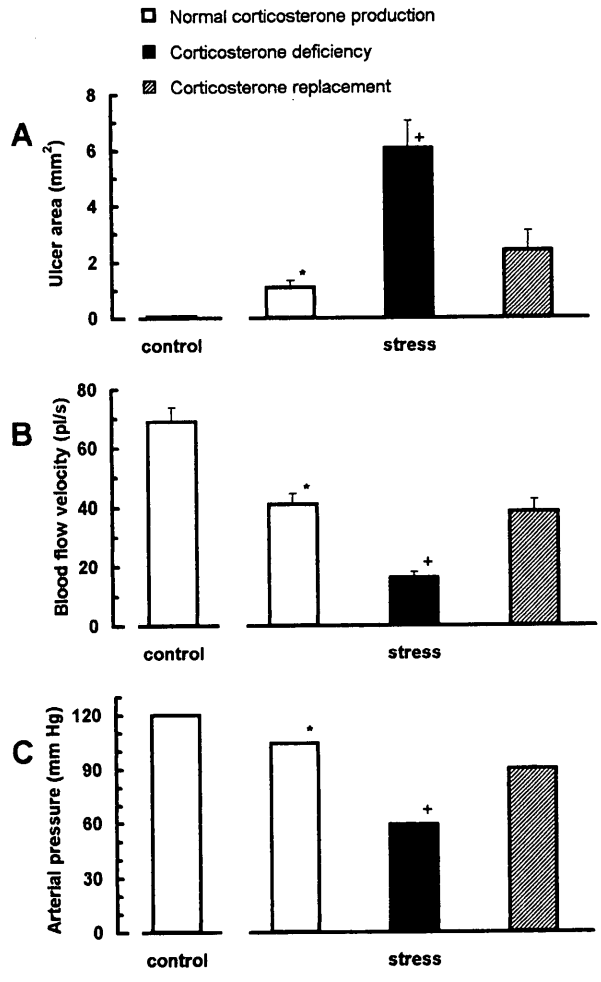

Fig. 4. Effects of corticosterone deficiency and corticosterone replacement on gastric ulceration (A), volume blood flow velocity (B), and arterial blood pressure (C) 3 hr after the onset of water-restraint stress. Values are means±SE; n=9-35/group for A, n=47-156/group for B, n=270-300/group for C. *P<0.05 compared with control; +P<0.05 compared with both the group with normal corticosterone production and the group with corticosterone replacement. The stress was produced in awake rats and blood flow velocity as well as blood pressure were evaluated in animals anesthetized in 3 hr after the onset of the stress.

water-restraint stress caused a decrease in this velocity. The deficiency of glucocorticoid production during stress potentiated the stress-induced decrease in blood flow velocity (Fig 4B). In stressed rats with glucocorticoid deficiency we observed a very slow red blood cell velocity and in some microvessels blood flow was even stopped. Replacing corticosterone significantly improved the blood flow in submucosal microvessels. After corticosterone replacement the average area of volume blood flow velocity was significantly large than that in rats with glucocorticoid deficiency (Fig. 4B).

The vascular pattern of microvessels situated just below the mucosal surface epithelial cells is shown on Fig. 2. The superficial mucosal capillaries present a honeycomb-like appearance because of their distribution around the openings of the gastric glands. This capillaries converge to form small venules (postcapillaries) that drain into collecting veins. Mean distance between two adjacent collecting veins estimated in our investigation was 407.4±14.1 μm (n=120). In control unstressed rats the average diameters of capillaries, postcapillaries and collecting veins were 6.0±0.1 μm (n=138), 13.4±0.4 (n=130) μm, 29.4±1.2 μm (n=138), respectively. The water-restraint stress induced significant alterations in the diameters of these superficial microvessels and the alterations were depended on the level of glucocorticoid production during the stress. Water-restraint produced a dilatation of mucosal microvessels. The average diameter of capillaries as well as of postcapillaries and collecting vein in stressed rats was significantly large than that in unstressed animals. The deficiency of glucocorticoids during water-restraint stress potentiated the stress-induced dilatation of each kind of superficial mucosal microvessels. Corticosterone replacement eliminated the effect of this deficiency (Fig. 5).

The water-restraint stress induced the reduction in systemic blood pressure a mean value of which was different in all investigated rats. Stressed rats with glucocorticoid deficiency had a dramatic fall in systemic blood pressure (Fig. 4C). In this case mean blood pressure was about 60 mm Hg. Replacing corticosterone again significantly improved a situation. The average area of systemic blood pressure in rats having corticosterone replacement was markedly larger than that in animals with glucocorticoid deficiency (Fig. 4C).

Discussion

The present results support our previous data about a gastroprotective action of glucocorticoids released in response to stress (5, 6, 7, 8, 9) and show that the protective influence of glucocorticoids on gastric mucosa during stress may involve the changes in gastric microcirculation.

The deficiency of glucocorticoid production during stress followed by corticosterone replacement was used as a method for a decision of the question formulated in this study. Water-restraint-induced glucocorticoid production was inhibited by delayed action after a single high dose of cortisol (300 mg/kg, ip) injected one week before the stress. The result of our previous study (10) showed that the inhibition of hypothalamo-pituitary-adrenocortical system at all three levels (hypothalamus, pituitary and adrenal) is the reason of a decrease in stress-induced glucocorticoid production after cortisol pretreatment.

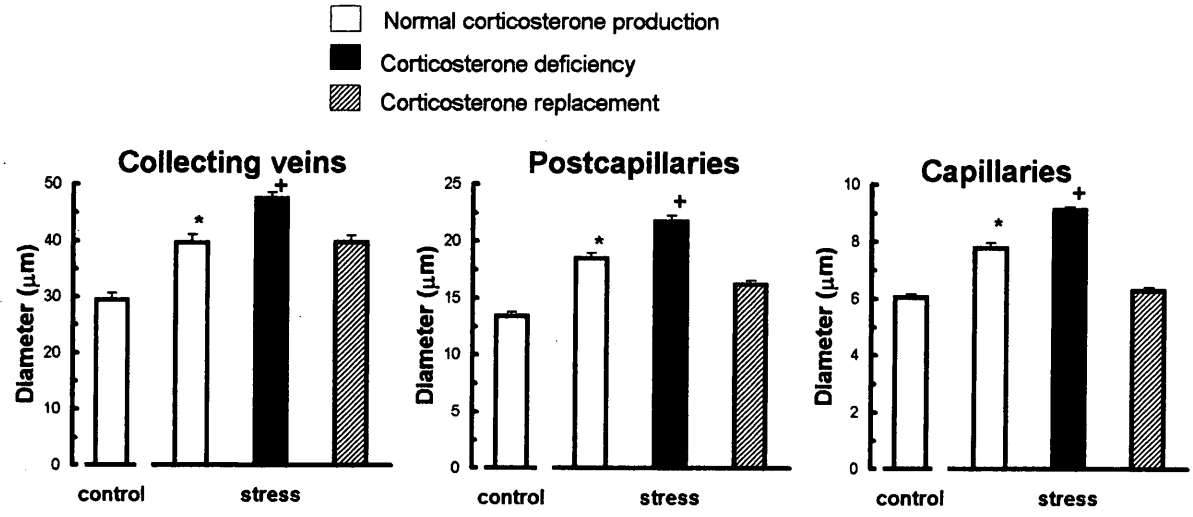

Fig. 5. Effects of corticosterone deficiency and corticosterone replacement on diameter of superficial mucosal microvessels: collecting veins, postcapillaries, capillaries - 3 hr after the onset of water-restraint stress. Values are means±SE; n=99-147/group for collecting veins, n=97-148/group for postcapillaries, n=83-130/group for capillaries. *P<0.05 compared with control; +P<0.05 compared with both the group with normal corticosterone production and the group with corticosterone replacement. The diameters were evaluated in rats anesthetized in 3 hr after the onset of the stress.

Cortisol pretreatment alone did not cause a pathological changes in stomach. It appears that excess amount of the hormone per se does not have a lasting ulcerogenic effect. However if water-restraint stress followed the administration of cortisol one week later the stress-induced ulceration was enhanced. These results are in agreement with our previous data obtained in cortisol treated rats during 24 h restraint or 3 h cold-restraint stress (5, 6). Replacing corticosterone attenuated the effect of glucocorticoid deficiency induced by cortisol on gastric ulceration in both our previous (5, 6) and the present studies. These investigations demonstrate that the deficiency of glucocorticoid production during stress promotes stress-induced gastric injury and together with our another results (9) suggest a gastroprotective role of these hormones.

To elucidate whether the gastroprotective action of glucocorticoids may involve an alteration in gastric microcirculation during stress we estimated the effect of the deficiency of glucocorticoid production followed by corticosterone replacement on those parameters of gastric microcirculation which are changed by stress. It is well known that an acute stress induces the significant changes in gastric blood flow as well as in diameter of superficial mucosal venous microvessels. It has been demonstrated that stress-induced decrease in gastric blood flow and an increase in diameter of superficial mucosal microvessels resulted in mucosal ischaemia (12, 21, 23, 25).

Our present findings are in good agreement with a data of literature about the decrease in gastric blood flow during an acute stress. In our experiments the water-restraint stress caused a decrease in red blood cell velocity as well as in volume blood flow velocity in submucosal vessels. The calculation of volume blood flow velocity in submucosal microvessels on the base of the red blood cell velocity and the diameter of the vessels was a correct step in our situation. Since, in this investigation, submucosal microvessel diameter was only about 6 μm and did not change with stress as well as with the alteration in glucocorticoid supply, the red blood cell velocity measured *in vivo* microscopy reflected blood flow in submucosal microvessels. As there are two parallel coupled circuits in the gastric wall (muscle and mucosa), with the submucosal microvasculature being in series with that of the mucosa (19, 20) it is clear that stress-induced decrease in submucosal blood flow have to coincide with that in mucosal blood flow. It was really so. Although our method did not permit the measurement of mucosal blood flow nevertheless we could see the fall in mucosal blood flow in stressed rats compared with that in control unstressed animals. In addition, it should be noted that mean value of volume blood flow velocity in submucosal vessels of unstressed rats measured in our experiments (69.1±4.8 pl/s) coincided with mean value of volume blood flow in mucosal superficial microvessels of unstressed rats measured by another method (75±7.4 pl/s) (16).

Results obtained in our study are also consistent with the data of literature about a dilatation of superficial mucosal venous microvessels during an acute stress (21, 23). In our experiments the water-restraint stress induced a significant increase in

diameters of mucosal capillaries, postcapillaries and collecting veins. Stress-induced superficial mucosal engorgement seems to be related to a local microcirculatory adjustment - e.g., possibly mucosal vein constriction causing mucosal drainage to slow (12). Mean diameter of each kind of mucosal microvessels of control unstressed rats registrated in our experiments coincided with that value estimated in a study by Holm-Rutili and Obrink (16).

The new fact concerning a stress-induced change in gastric microcirculation which was discovered in the present study consist in the dependence of these changes upon glucocorticoid supply during stress. Our data show that the deficiency of glucocorticoid production during water-restraint stress promoted the stress-induced decrease in blood flow velocity and the stress-induced dilatation of superficial mucosal microvessels, and corticosterone replacement eliminated these effects. This data suggest that glucocorticoids released during water-restraint stress maintain a gastric blood flow.

The data of the present study demonstrated that the impairment of gastric microcirculation was followed by the increase in gastric ulceration. Water-restraint stress induced the decrease in gastric blood flow and the dilatation of mucosal microvessels which were followed by appearance of gastric injury. The same stress produced in rats with deficiency of glucocorticoid supply potentiated both the impairment of gastric microcirculation and gastric ulcer formation. Corticosterone replacement improved both the gastric microcirculation and the gastric mucosal integrity. We should not prove a relationship between gastric microcirculation and gastric ulceration. Many studies have demonstrated a relationship between reduced mucosal blood flow and gastric injury in stressed rats (12, 13, 14, 23, 24, 25). In particular, there is evidence that mucosal ischemia is one of the main reason of gastric ulceration during water restraint stress (25). Controversially, increasing mucosal blood flow by pretreating animals with some drugs protected against gastric mucosal injury (4). These facts permit to conclude that the improvement of gastric microcirculation by glucocorticoids released to response a stress have an important significance for the realization of gastroprotective effect of these hormones.

To understand the mechanisms of protective influences of glucocorticoids on gastric microcirculation is an important area for the further study. Nevertheless, the present investigation show that the reduction in systemic blood pressure is associated with the decrease in gastric blood flow. The more reduction in blood pressure was followed by the more decrease in gastric blood flow. Mean systemic blood pressure in stressed rats with glucocorticoid deficiency was about 60 mm Hg and these animals had a very low gastric blood flow velocity. Corticosterone replacement increased both systemic blood pressure and gastric blood flow. Our finding about the relationship between systemic blood pressure and gastric blood flow is in a good agreement with the results obtained by other investigators (see: Ref. 11). There is evidence of the linear correlation between mucosal blood flow and graded systemic hypotension. It was hypothesized that blood flow to a stomach as to a nonessential organ decreases proportionately more rapidly and at an earlier stage of graded hypotension, in order to help maintain blood flow to essential organs such as the brain and kidney (11).

In conclusion, the present study showed that gastric microcirculation represents a very important factor for the realization of gastroprotective effect of glucocorticoids released during stress. In accordance with our data the protective action of glucocorticoids against stress-induced gastric mucosal ulceration may be provided by the maintenance of gastric blood flow.

Acknowledgment

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