Gastroprotective Role of Glucocorticoid Hormones

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Abstract. Gastric ulcer disease remains widespread; a stressful lifestyle and nonsteroidal antiinflammatory drugs (NSAIDs) make significant contributions to this pathological situation. The findings overviewed here support the idea that glucocorticoid hormones released in response to acute stress or NSAIDs act as gastroprotective substances and exert many of the same actions in the stomach as prostaglandins (PGs) and nitric oxide (NO) as well as capsaicin-sensitive afferent neurons. Glucocorticoids exert a gastroprotective effect by both maintaining local defensive factors (mucosal blood flow and mucus production) and inhibiting pathogenic elements (gastric motility and microvascular permeability). Furthermore, they exert gastroprotective actions in cooperation with PGs, NO, and the afferent neurons; and their compensatory action is observed when the protective mechanism provided by either of these factors is impaired. The gastroprotective action of glucocorticoids is also associated with maintenance of general body homeostasis, including blood glucose levels and systemic blood pressure. In conclusion, glucocorticoids released in response to acute stress or NSAIDs are naturally occurring protective factors that play an important role in maintenance of the gastric mucosal integrity. This led us to re-evaluate the traditional paradigm that glucocorticoid hormones produced during activation of the hypothalamic-pituitary-adrenocortical axis are ulcerogenic in the stomach.

Keywords: hypothalamic-pituitary-adrenocortical axis, glucocorticoid hormone, stress- and nonsteroidal antiinflammatory drug (NSAID)-induced gastric erosion, gastroprotection

Introduction

Gastric ulcer disease remains widespread; a stressful lifestyle and non-steroidal antiinflammatory drugs (NSAIDs) make significant contributions to this pathological situation (1, 2). Despite indubitable advances in elucidation of the pathogenesis of gastric ulceration, there are gaps in our understanding of ulcerogenesis, particularly the role of the key hormonal system of adaptation: the hypothalamic-pituitary-adrenocortical (HPA) axis.

Glucocorticoid hormones released during acute stress-induced activation of the HPA axis help the body overcome negative effects of stress stimuli (3). Despite this knowledge, it has been generally accepted for several decades that glucocorticoids released during stress cause a ulcerogenic response in the stomach, and stress-induced activation of the HPA axis is considered a pathogenic component of this response.

As the widely held view about the ulcerogenic role of glucocorticoids released during stress is difficult to reconcile with the adaptive role of HPA axis hormones, we designed experiments to clarify the validity of this view. The results obtained do not support the traditional paradigm and suggest that glucocorticoids released during acute activation of the HPA axis are important gastroprotective factors. In this article, we review our recent publications on the role of glucocorticoids in gastroprotection and discuss possible mechanisms...
and he concluded that the formation of "stress ulcers" in these animals, "stress ulcers" were not prevented, animals by Selye himself, who observed that although gated in hypophysectomized and adrenalectomized gastric ulcerogenesis. This possibility was also investigated by hypophysectomized and adrenalectomized animals by Selye himself, who observed that although stress-induced thymic-lymphatic atrophy and adrenal hypertrophy) and the role of the hypothalamus in activating the hypophysis, which, in turn, stimulates the adrenals to produce corticoids (4). From the very outset, researchers have focused on the idea that stress-generated glucocorticoids are causally related with gastric ulcerogenesis. This possibility was also investigated in hypophysectomized and adrenalectomized animals by Selye himself, who observed that although stress-induced thymic-lymphatic atrophy was inhibited in these animals, “stress ulcers” were not prevented, and he concluded that the formation of “stress ulcers” depends on not only the pituitary-adrenal axis but other factors as well. He also proposed that neurostimulators play a major role in stress-induced ulcerogenesis, although high levels of corticoids in blood could be a sensitizing factor (4). Weiss (5) found in rats that the severity of stress-induced ulceration is positively correlated with the level of corticosterone in plasma and proposed that “steroids, in quantities that the animal is capable of secreting, may contribute to the production of ulcers”. Further support for this idea came from the observation that animals with hippocampal lesions had increased levels of plasma corticosterone and developed more gastric ulcers during stress (6). One approach used to support the view that stress-generated glucocorticoids are ulcerogenic was a groundless extrapolation of the ulcerogenic properties of exogenous glucocorticoids observed at high pharmacological doses (see ref. 7) to the properties of endogenous glucocorticoids released during stress.

From the beginning (8), we have focused on the idea that glucocorticoids released during acute stress also have an adaptive effect on the stomach and, therefore, are gastroprotective rather than ulcerogenic. To test this hypothesis, we examined the effect of glucocorticoid deficiency or the glucocorticoid-receptor antagonist RU-38486 on water and immersion-restraint-induced or cold-restraint-induced gastric erosion in rats (7 – 9). Different approaches were used to inhibit the stress-induced release of corticosterone: the inhibition of corticotropin-releasing hormone (CRH) synthesis in the hypothalamic paraventricular nucleus by intrahypothalamic implantation of dexamethasone, the immunoneutralization of adrenocorticotropic hormone (ACTH) by pretreatment with ACTH antiserum, and the inhibition of the HPA axis at the hypothalamic and the pituitary levels by pretreatment with a pharmacological dose of cortisol one week before stress. Corticosterone replacement, that is, the injection of corticosterone at a dose mimicking the stress-induced rise in corticosterone (4 mg/kg) 15 min before stress, was used in our experiments (Fig. 1).

Intrahypothalamic dexamethasone implantation significantly decreased the stress-induced increase in corticosterone and markedly provoked the gastric erosion caused by stress. Corticosterone replacement prevented the aggravating effect of dexamethasone on the ulceration (Fig. 1A). ACTH antiserum administered shortly before cold-restraint stress decreased the release of corticosterone in response to stress and enhanced the severity of the gastric erosion (Fig. 1B) (9). Pretreatment with glucocorticoid (cortisol) at a pharmacological dose caused an inhibition of the HPA axis at the hypothalamic and pituitary levels via a negative feedback mechanism and resulted in a long-lasting decrease in the stress-induced rise in corticosterone levels (8, 10). It is important to emphasize that animals were stressed one week after the treatment with cortisol when the exogenous hormone had already been eliminated but the corticosterone response to stress was still inhibited. The cortisol pretreatment increased the ulcerogenic action in different models of stress, and acute corticosterone replacement that mimicked the stress-induced corticosterone response reduced gastric erosion in rats with a inhibited HPA axis (Fig. 1C) (7, 8). These results support the idea that the gastric ulcerogenic response to stress is potentiated by a reduction of stress-induced glucocorticoid production. It is important to note that each of our models induced at least a 50% inhibition of the corticosterone increase, as was estimated from the area under the corticosterone curve (9). A slight reduction of the stress-induced corticosterone level by metyrapone treatment did not influence gastric erosion caused by stress (11). Glucocorticoid antagonists offer another way to demonstrate the role of the stress-induced rise in corticosterone in the gastric ulcerogenic response to stress. It was found that the occupation by RU-38486 of glucocorticoid receptors during stress aggravates stress-induced gastric erosion (9). Therefore, the reduction in the stress-induced release, or actions of corticosterone, decreases the ability to protect the gastric mucosa from injury during stress. It is suggested that an acute increase in
gastroprotective action of glucocorticoid hormones released during acute stress

Various stressful stimuli activate the HPA axis, and consequently, the production of glucocorticoids and severe stress stimuli may also induce gastric erosion, called “stress ulcers”. Hans Selye, the “Father” of the field of research into stress, attracted attention to these signs of stress. His greatest contributions were the demonstration of the stress triad (gastrointestinal ulceration, thymic-lymphatic atrophy, and adrenal hypertrophy) and the role of the hypothalamus in activating the hypophysis, which, in turn, stimulates the adrenals to produce corticoids (4). From the very outset, researchers have focused on the idea that stress-generated glucocorticoids are causally related with gastric ulcerogenesis. This possibility was also investigated in hypophysectomized and adrenalectomized animals by Selye himself, who observed that although stress-induced thymic-lymphatic atrophy was inhibited in these animals, “stress ulcers” were not prevented, and he concluded that the formation of “stress ulcers” depends on not only the pituitary-adrenal axis but other factors as well. He also proposed that neurostimulators play a major role in stress-induced ulcerogenesis, although high levels of corticoids in blood could be a sensitizing factor (4). Weiss (5) found in rats that the severity of stress-induced ulceration is positively correlated with the level of corticosterone in plasma and proposed that “steroids, in quantities that the animal is capable of secreting, may contribute to the production of ulcers”. Further support for this idea came from the observation that animals with hippocampal lesions had increased levels of plasma corticosterone and developed more gastric ulcers during stress (6). One approach used to support the view that stress-generated glucocorticoids are ulcerogenic was a groundless extrapolation of the ulcerogenic properties of exogenous glucocorticoids observed at high pharmacological doses (see ref. 7) to the properties of endogenous glucocorticoids released during stress.

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cortisol protects the stomach against stress-induced injury.

Two most common stress ulcerogenic techniques in current use are water and immersion-restraint and cold-restraint. In our experiments rats were restrained for 3 h either in a cold room (temperature 4°C) or in water (temperature 18°C). We did not observe significant differences between these models regarding both stress-induced cortisol rise and area of gastric erosion (9). Although water and immersion-restraint...
and cold-restraint stress methods are different in the temperature used, nevertheless hypothermia is the leading ulcerogenic factor in both cases. Accordingly to our data, the beneficial effect of corticosterone produced during water and immersion-restraint and cold-restraint stress may be functionally associated with prevention of lowering of body temperature.

There is evidence that the decrease in submucosal and mucosal blood flow during stress is an important factor leading to mucosal ischemia, impairment of tissue resistance, and subsequent ulceration in stressed animals (12). Using in vivo microscopy to directly visualize the gastric microcirculation, we examined the effects of a deficiency of stress-induced glucocorticoid production as well as corticosterone replacement in anesthetized rats after ulcerogenic stress. The deficiency of glucocorticoids during water immersion-restraint stress promoted the stress-induced decrease of blood flow velocity in submucosal and mucosal microvessels, the effect being prevented by corticosterone replacement (13, 14). These results suggest that the gastroprotective actions of glucocorticoids during stress may be partly due to the maintenance of gastric mucosal blood flow that may be brought about by the effect on arterial blood pressure (13, 14).

**Gastroprotective action of glucocorticoids produced during NSAID treatment**

Similar to stress, NSAID treatment may activate the HPA axis (15, 16). Administration of both indomethacin (25 – 35 mg/kg, s.c.) and aspirin (40 mM, p.o. with HCl) induced a release of corticosterone, which in turn may help protect the gastric mucosa against NSAIDs. Indeed, adrenalectomy prevented NSAID-induced corticosterone release and markedly worsened the gastric erosion caused by NSAIDs. Acute corticosterone replacement, mimicking the indomethacin- and aspirin-induced rise in corticosterone, also prevented the aggravation of gastric ulcers generated by adrenalectomy (Fig. 2: A and B) (16). The aggravation of NSAID-induced gastric erosion was also demonstrated in another model of glucocorticoid deficiency where the NSAID-induced corticosterone rise was prevented by pharmacological blockade of the HPA axis (15, 17). Likewise, pretreatment of the animals with the glucocorticoid-receptor antagonist RU-38486 significantly aggravated the severity of gastric ulcers induced by indomethacin as well as aspirin (16). It is thus assumed that endogenous glucocorticoids released during NSAID treatment increase the resistance of the gastric mucosa to NSAID-induced injury.

The gastric ulcerogenic properties of NSAIDs limit the use of these drugs for the treatment of chronic inflammatory disorders, and it has been considered that combined treatment with therapeutic doses of glucocorticoid increases the risk of gastric ulceration (18). The increased risk of adverse gastric reactions should be considered when NSAIDs are used in patients with...
impaired glucocorticoid production.

Endogenous glucocorticoids may have a permissive role in allowing gastroprotective mechanisms to exert their full potential. This action was suggested in gastric mucosal protection against aspirin-induced erosion induced by cimetidine (19) or interleukin-1 (20). Likewise, a normal basal production of glucocorticoids is also important for the gastric mucosa to resist indomethacin (21)- or aspirin (20)-induced damage. Furthermore, both aspirin and indomethacin at ulcerogenic doses stimulate glucocorticoid production to cause an acute elevation of glucocorticoid content in the physiological range, which in turn protects against gastric damage induced by these NSAIDs.

The mechanism by which indomethacin induces gastric injury is generally considered to involve gastric hypermotility, microcirculatory disturbances, neutrophil-endothelial cell interactions, and superoxide radicals (22, 23). Among them, gastric hypermotility is a key element in the pathogenesis of these lesions (21). Mersereau and Hinchey (24) reported a role for the glycoprivic response in the mechanism of gastric hypermotility induced by NSAIDs. To clarify the mechanisms underlying the gastroprotective action of glucocorticoids against indomethacin-induced injury, we investigated the effect of adrenalectomy with or without corticosterone replacement on blood glucose levels, gastric motility, microvascular permeability, blood flow velocity in gastric submucosal and mucosal microvessels, and mucus secretion before and after the administration of indomethacin at an ulcerogenic dose (14, 17, 25). Indomethacin caused gastric erosion in sham-operated rats, with an increase in gastric motility and microvascular permeability as well as a decrease in the blood glucose level, mucus secretion, and blood flow velocity in gastric submucosal and mucosal microvessels (Fig. 2). Adrenalectomy significantly worsened the lesions and potentiated these functional disorders. Adrenalectomized rats given indomethacin showed a decrease in blood glucose levels, gastric mucus content, and blood flow velocity in gastric microvessels and an increase in gastric motility index and microvascular permeability, resulting in a marked enhancement of the gastric lesion score when compared to other experimental groups (Fig. 2). All changes observed in adrenalectomized rats were prevented by supplementation of corticosterone at a dose mimicking the indomethacin-induced rise in corticosterone, whereas the protective effect of corticosterone was attenuated by a glucocorticoid-receptor antagonist RU-38486. It is assumed that the gastroprotective action of endogenous glucocorticoids may be provided by their support of glucose homeostasis and inhibitory effects on enhanced gastric motility and microvascular permeability as well as maintaining mucus production and blood flow in gastric microvessels (Fig. 2).

These data together with our previous findings support the idea that glucocorticoids released during activation of the HPA axis caused by stress or NSAIDs as well as other ulcerogenic stimuli (10) act as gastroprotective hormones.

Compensatory gastroprotective role of glucocorticoids during the deficiency of other gastroprotective factors

Both humoral and neuronal factors, such as prostaglandins (PGs), nitric oxide (NO), and capsaicin-sensitive afferent neurons, play a pivotal role in the defense against gastric mucosal injury (23, 26, 27). They contribute to gastroprotection by modulating mucosal blood flow, mucus secretion, and repair of injured gastric mucosa. We showed that glucocorticoids released in response to ulcerogenic stimuli are naturally occurring gastroprotective factors and exert many of the same actions in the stomach as PGs, NO, and capsaicin-sensitive afferent neurons. This has prompted us to consider the interaction between glucocorticoid hormones and other protective factors in the maintenance of gastric mucosal integrity.

We then compared the effects of the drug-induced inhibition of PG and NO production or the desensitization of capsaicin-sensitive sensory neurons on the gastric mucosa in rats deficient in or with normal glucocorticoids, under normal or ulcerogenic conditions. Indomethacin at 35 mg/kg (s.c.) was used as an ulcerogenic stimulus. The glucocorticoid deficiency was caused by adrenalectomy one week before the experiment. Two kinds of corticosterone replacement were used in adrenalectomized rats. Indomethacin at a nonulcerogenic dose (5 mg/kg, i.p.) or N\textsuperscript{6}-nitro-L-arginine methyl ester (L-NAME) (50 mg/kg, s.c.) was acutely given to inhibit PG and NO production, respectively. For the desensitization (functional ablation) of capsaicin-sensitive afferent neurons, rats were given subcutaneous injections of capsaicin in 3 consecutive doses of 20, 30, and 50 mg/kg (28). Adrenalectomy by itself did not cause damage in the stomach. Neither inhibition of PG or NO, nor sensory deafferentation by itself provoked any damage in the gastric mucosa of sham-operated rats. However, both of these treatments damaged the gastric mucosa in adrenalectomized rats, and all of these responses were prevented by corticosterone in drinking water at a concentration mimicking the basal corticosterone level in normal rats (28).

Indomethacin-induced gastric erosion was aggravated
to a similar extent by adrenalectomy, inhibition of NO production, or desensitization of capsaicin-sensitive afferent neurons. These data suggest that the role of glucocorticoid hormones in protection of the gastric mucosa against indomethacin is no less significant than that of NO or capsaicin-sensitive afferent neurons. The combination of adrenalectomy with inhibition of NO production or sensory deafferentation markedly potentiated the aggravating effect of these treatments by themselves on indomethacin-induced gastric erosions: the mean erosion area was increased approximately 5 or 10 times, respectively. Corticosterone at a dose mimicking the indomethacin-induced corticosterone rise totally prevented the aggravating effect of adrenalectomy in these experiments (28). These results demonstrate for the first time that the effect of inhibition of NO production or sensory deafferentation on indomethacin-induced gastric erosion is significantly modified by glucocorticoid deficiency. This, in turn, suggests the important role of glucocorticoid hormones in the maintenance of gastric mucosal integrity under adverse conditions when the gastroprotective action of NO or capsaicin-sensitive neurons is impaired.

The most profound aggravation in the gastric ulcerogenic response was observed when adrenalectomy was performed together with desensitization of capsaicin-sensitive afferent neurons. Glucocorticoids (29) and these afferent neurons (30) are known to be involved in glucostasis during hypoglycemia. Moreover, both of these factors contribute to gastroprotection through a beneficial influence on gastric mucosal blood flow (13, 14, 27). The simultaneous removal of the beneficial action of both factors on these targets might explain why severe gastric damage occurs in adrenalectomized rats with desensitization of capsaicin-sensitive afferent neurons. It is assumed that the compensatory protective action of glucocorticoids against indomethacin in sensory deafferentated rats is provided by their maintenance of gastric blood flow (31) and glucose homeostasis (28).

Thus, these results suggest a pivotal compensatory role of glucocorticoids in the maintenance of gastric mucosal integrity in the case of impaired gastroprotective mechanisms provided by PGs, NO, and capsaicin-sensitive afferent neurons. The compensatory gastroprotective role of glucocorticoids during PG deficiency (16) or desensitization of capsaicin-sensitive afferents (28) may be provided through enhancement of their production in these situations. We also showed that glucocorticoid deficiency, in turn, induces a compensatory enhancement in PG production in the stomach through cyclooxygenase (COX)-2 expression (32).

It has been suggested that “PGs, NO, and sensory neuropeptides act in concert in the maintenance of mucosal viability” (33). This suggestion was confirmed and reinforced by other investigations. Our data add new information to such a “concerted” modulation of the gastric mucosal integrity and suggest that glucocorticoids are also important participants in this modulation.

Summary and conclusions

An acute stress-induced increase of glucocorticoids has a gastroprotective action against stress-induced gastric injury but is not ulcerogenic, as it has generally been considered for some decades. Beneficial actions of endogenous glucocorticoids released during acute stress on the stomach are opposite to the harmful actions of exogenous glucocorticoids used at pharmacological doses. NSAIDs, similar to stress, induce an increase in glucocorticoid production that in turn helps the gastric mucosa to resist the harmful actions of these drugs. Gastroprotective effects of glucocorticoids may be mediated by multiple actions, including maintenance of gastric mucosal blood flow, mucus production, and attenuation of enhanced gastric motility and microvascular permeability. In addition, glucocorticoids released during activation of the HPA axis may contribute to protection of the gastric mucosa by maintaining general body homeostasis, including glucose levels and systemic blood pressure, which could be fundamental to their beneficial influence on gastric mucosal integrity. Furthermore, glucocorticoids may cooperate with PGs, NO, and capsaicin-sensitive afferent neurons in the modulation of gastric mucosal integrity. Glucocorticoid hormones exert a compensatory gastroprotective role in the case of impaired gastroprotective mechanisms provided by PGs, NO, and capsaicin-sensitive sensory neurons. In conclusion, these findings indicate that activation of the HPA axis could be considered an important gastroprotective factor.

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