Glucocorticoids are gastroprotective under physiologic conditions

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Abstract: Stress may contribute to the development and progression of gastrointestinal disorders. Activation of the hypothalamic–pituitary–adrenocortical (HPA) axis is one of the main characteristics of stress. For several decades it was generally accepted that glucocorticoids released during stress are ulcerogenic hormones. We designed some experimental studies in rats to clarify the validity of this widely held view. To achieve this goal, we examined the effect of glucocorticoid deficiency followed by corticosterone replacement or the glucocorticoid receptor antagonist, RU-38486, on stress-induced gastric erosion and the parameters of gastric function in rats. The data obtained shows that the reduction in the stress-induced corticosterone release, or its actions, aggravates stress-caused gastric erosion. It is suggested that an acute increase in corticosterone during stress protects the stomach against stress-induced injury. According to our results, various ulcerogenic stimuli, similar to stress, induce an increase in corticosterone that helps the gastric mucosa to resist against a harmful action of ulcerogenic stimuli. Glucocorticoids exhibit their gastroprotective effect by both maintaining local defensive factors and inhibiting pathogenic elements. Furthermore, the contribution of glucocorticoids to gastroprotection is tightly related to their contribution to general body homeostasis. Glucocorticoids provide gastroprotective actions in co-operation with prostaglandins, nitric oxide and capsaicin-sensitive sensory neurons. The results obtained do not support the traditional paradigm and suggest that glucocorticoids released during acute activation of the HPA axis are naturally occurring gastroprotective factors. In this article, we review our recent publications on the role of glucocorticoids in gastroprotection.

Keywords: anti-inflammatory drugs, gastric erosion, gastroprotection, glucocorticoids, hypothalamic–pituitary–adrenocortical axis, stress

Introduction

A stressful lifestyle and nonsteroidal anti-inflammatory drugs (NSAIDs) make significant contributions to gastric ulcer disease, which remains widespread [Laine *et al.* 2008]. Despite indubitable advances in elucidation of the pathogenesis of gastric ulceration, there are gaps in our understanding of ulcerogenesis, particularly with regards to the role of the key hormonal system of adaptation, the hypothalamic–pituitary–adrenocortical (HPA) axis, and consequently glucocorticoid hormones.

Glucocorticoid hormones and gastric ulceration have been discussed in many contexts. The action of acute and chronic treatment of patients or experimental animals with glucocorticoids as well as the effects of basal and stress-induced

glucocorticoid production on the gastric mucosa have been considered. Although there is a long-standing debate over whether glucocorticoid therapy by itself leads to peptic ulcer disease in humans [Olsen *et al.* 2010; Luo *et al.* 2009], it is established that administration of glucocorticoids to experimental animals can result in an acute gastric erosion formation [Takeuchi *et al.* 2008; Bandyopadhyay *et al.* 1999; Black, 1988]. At the same time, in some cases, the administration of glucocorticoids to animals can attenuate gastric erosion formation [Filaretova *et al.* 2009b; McCafferty *et al.* 1995; Derelanko and Long, 1982]. It has been shown that pretreatment with prednisolone [Derelanko and Long, 1982] or dexamethasone [Filaretova *et al.* 2009b; McCafferty *et al.* 1995] may protect the stomach from ethanol- or NSAID-induced

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injury, respectively. It is also known that basal glucocorticoid production contributes to the maintenance of the gastric mucosal integrity [Suzuki *et al.* 1999; Takeuchi *et al.* 1989]. The 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 (PGs), sulfhydryls, cimetidine [Szabo *et al.* 1983] or interleukin-1 [Perretti *et al.* 1992]. The most controversial question is about the action of stress-produced glucocorticoids. Based on the notion that exogenous glucocorticoids used at pharmacological doses have ulcerogenic properties, the increase in the levels of glucocorticoids during stress was also considered to be an ulcerogenic factor. Also, it is known that glucocorticoid hormones released during acute stress-induced activation of the HPA axis help the body to overcome the negative effects of stress stimuli [Munck *et al.* 1984]. Despite this knowledge, it has been generally accepted for several decades that stress-produced glucocorticoids cause an 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 the HPA axis hormones, we designed experiments in rats 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.

Gastroprotection by glucocorticoids 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 erosions, known as '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, thymico-lymphatic atrophy, and adrenal hypertrophy) and of the role of the hypothalamus in activating the hypophysis, which, in turn, stimulates the adrenals to produce corticoids [Selye, 1967]. 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 thymico-lymphatic atrophy was inhibited in these animals, 'stress ulcers' were not prevented, and 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 [Selye, 1967]. Weiss found that the severity of stress-induced ulceration in rats 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' [Weiss, 1971]. 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 [Murphy *et al.* 1979]. 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 to the properties of endogenous glucocorticoids released during stress.

From the beginning [Filaretova, 1990], 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 [Filaretova, 2006, 1990; Filaretova *et al.* 1998]. Different approaches were used to inhibit the stress-induced release of corticosterone: the inhibition of corticotropin-releasing hormone synthesis in the hypothalamic paraventricular nucleus by intrahypothalamic implantation of dexamethasone, the immunoneutralization of adrenocorticotrophic 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 1 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.

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. 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 [Filaretova *et al.* 1998]. 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 [Filaretova, 2006; Filaretova *et al.* 2001a]. It is important to emphasize that animals were stressed 1 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 an inhibited HPA axis [Filaretova, 2006, 1990]. These results support the idea that the gastric ulcerogenic response to stress is potentiated by a reduction of stress-induced glucocorticoid production. 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 cold-restraint stress aggravates the stress-induced gastric erosion [Filaretova *et al.* 1998]. 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 corticosterone protects the stomach against stress-induced injury.

Further support for the point of view that glucocorticoids released during acute stress are naturally occurring gastroprotective factors came from our results demonstrated for the first time that glucocorticoids contribute to the

gastroprotective effect of preconditioning mild cold-restraint stress [Filaretova *et al.* 2008].

It should be emphasized that our studies on the mode of gastroprotection by glucocorticoids have been performed on animals during acute ulceration. The effects of glucocorticoids on the gastric mucosa during chronic stress conditions may be different from those observed in acute experiments.

Gastroprotection by glucocorticoids during treatment with NSAIDs

According to our results [Filaretova *et al.* 2002c, 2001b], NSAID treatment, similar to cold- and water-restraint stress, may activate the HPA axis. Administration of both indomethacin and aspirin 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 [Filaretova *et al.* 2002c]. 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 [Filaretova *et al.* 2005, 2001b]. Likewise, pretreatment of the animals with RU-38486, the glucocorticoid receptor antagonist, significantly aggravated the severity of gastric erosion induced by indomethacin as well as aspirin [Filaretova *et al.* 2002c]. 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 [Hawkey, 2000]. The results obtained in our studies [Filaretova *et al.* 2005, 2002c, 2001b] suggest that 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 [Szabo *et al.* 1983] or interleukin-1 [Perretti *et al.* 1992]. Likewise, a normal basal production of glucocorticoids is also important for the gastric mucosa to resist indomethacin- [Takeuchi *et al.* 1989] or aspirin-induced damage [Perretti *et al.* 1992]. 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.

These data together with our previous findings support the point of view that glucocorticoids released during acute activation of the HPA axis caused by stress or NSAIDs as well as other ulcerogenic stimuli [Filaretova *et al.* 2001a] act as gastroprotective hormones. From the beginning [Filaretova, 1990], we have focused on the hypothesis that glucocorticoids released during stress also have an adaptive effect on the stomach. The results obtained in our studies confirm this hypothesis and furthermore demonstrate that glucocorticoids released in response to NSAIDs or other ulcerogenic stimuli also have an adaptive effect on the stomach. In turn, it means that the HPA axis activation is a physiologic gastroprotective component of acute stress response.

It is paradoxical, but to understand physiologic processes/mechanisms we used pathological models: the models of acute ulceration (for example, stress- or indomethacin-induced gastric lesions). In this way, we were able to verify the effects of glucocorticoids on a resistance of the gastric mucosa to injury. Using these models we demonstrated that the increase in glucocorticoid production helps the gastric mucosa to resist the ulcerogenic action of stress or other stimuli. Glucocorticoids released in response to these ulcerogenic stimuli attenuate their harmful action on the gastric mucosa. Moreover, according to our data weak stimuli do not damage the gastric mucosa by way of a physiologic gastroprotective effect of glucocorticoids released in response to these stimuli [Filaretova *et al.* 2001a; Filaretova, 1990]. Indeed, we showed that in rats with glucocorticoid deficiency a normally nonulcerogenic stress stimulus turns into

an ulcerogenic one [Filaretova, 1990]. Another striking demonstration of the gastroprotective role of glucocorticoids in physiological conditions is the participation of glucocorticoids in the gastroprotective effects of preconditioned stress [Filaretova *et al.* 2008].

Mechanisms of gastroprotective action of glucocorticoids

Maintenance of gastric blood flow is important to protect the gastric mucosa from various deleterious factors. 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 [Guth, 1992]. Using *in vivo* microscopy for the direct visualization of gastric microcirculation, 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 glucocorticoids during water immersion-restraint stress promoted the stress-induced decrease of blood flow velocity in submucosal and mucosal microvessels, and corticosterone replacement eliminated this effect [Filaretova *et al.* 2004, 1999]. These data suggest that the gastroprotective actions of glucocorticoids during stress may be provided by the maintenance of gastric blood flow that may be brought about by the effect on arterial blood pressure [Filaretova *et al.* 2004, 1999].

The mechanism by which indomethacin induces gastric injury is generally considered to involve deficiency of PGs, yet it has proven to be more complicated than expected and involves multiple, closely interacting elements such as gastric hypermotility, microcirculatory disturbances, neutrophil–endothelial cell interactions, and superoxide radicals, in addition to PG deficiency [Wallace, 1997; Takeuchi *et al.* 1991]. Among them, gastric hypermotility is a key element in the pathogenesis of these lesions [Takeuchi *et al.* 1991]. Mersereau and Hinchey reported a role for the glycoprivic response in the mechanism of gastric hypermotility induced by NSAIDs [Mersereau and Hinchey, 1982]. 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 a ulcerogenic dose [Filaretova *et al.* 2005, 2004, 2002b]. 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. 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 sham-operated indomethacin-treated group. 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 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 [Filaretova *et al.* 2002b].

Interactions at the leukocyte-endothelium interface are also critical in the pathogenesis of NSAID-induced gastric mucosal injury. Adherence of neutrophils to the vascular endothelium is an early and critical event in the pathogenesis of gastric injury induced by NSAIDs [Wallace, 1997; Wallace *et al.* 1993]. Glucocorticoids as anti-inflammatory hormones may contribute to gastroprotection by inhibition of neutrophil adherence. Glucocorticoids are known to downregulate expression of adhesive molecules such as intercellular adhesion molecule-1 (ICAM-1) [Papi *et al.* 2000]. Some of the anti-inflammatory effects of glucocorticoids, including inhibition of neutrophil adherence, are mediated via the release of annexin-1, previously referred as lipocortin 1. Pretreatment with glucocorticoids has been shown to prevent NSAID-induced neutrophil adherence and, in turn, to protect the stomach from injury [McCafferty *et al.* 1995]. Annexin-1 plays an important role in mediating the gastroprotective effects of

glucocorticoids in a model of NSAID-induced gastric damage [Zanardo *et al.* 2005]

The predominant mode of action of glucocorticoids involves regulation of gene expression via the glucocorticoid receptor. The glucocorticoid receptor is a member of a superfamily of ligand-inducible transcription factors that control a variety of physiological functions. The glucocorticoid receptor is ubiquitously expressed in most tissues in rats [Lu and Cidlowski, 2005], and in the gastric mucosa it was identified mainly in parietal cells [Kanemasa *et al.* 1999]. Unliganded glucocorticoid receptors are predominantly localized within the cytoplasm but rapidly and efficiently translocate into the nucleus following hormone binding to bind glucocorticoid-responsive elements at regulatory regions of target genes [Heitzer *et al.* 2007]. RU-38486 is known to bind with a high affinity to type II glucocorticoid receptors and may influence peripheral as well as central glucocorticoid receptors [Tempel *et al.* 1993; Moguilewski and Philibert, 1984]. In the simultaneous presence of glucocorticoids and the antagonist *in vivo*, glucocorticoid receptors are predominantly occupied by the antagonist [Alexandrova, 1994]. The RU-38486-glucocorticoid receptor complex is incapable of nuclear translocation and does not produce a biological effect [Moguilewski and Philibert, 1984]. For this reason, RU-38486 can be a tool for investigating modes of glucocorticoid action. We used RU-38486 to evaluate the role of stress- or NSAID-induced corticosterone increase in gastric erosion. Administration of RU-38486 significantly aggravated water-restraint stress- and indomethacin- or aspirin-induced gastric erosion [Filaretova *et al.*, 2002c, 1998]. Moreover, RU-38486 prevented beneficial effects of corticosterone replacement on the gastric mucosa in adrenalectomized rats [Filaretova *et al.* 2002b]. We believe these results support the gastroprotective role of glucocorticoids released during stress and NSAID action. These data also suggest that the gastroprotective action of glucocorticoids may occur, at least partly, through the classical genomic mechanism. The use of RU-38486 clarifies the receptor action and proves that gastroprotective effect is mediated by glucocorticoid II receptors. There is also evidence that glucocorticoids can act through nongenomic pathways [Whitehouse, 2011]. We do not rule out that nongenomic mechanisms may also be involved in gastroprotective action of glucocorticoids. There are multiple targets where glucocorticoids

can exert their beneficial influence on the gastric mucosa. We demonstrated that the gastroprotective action of glucocorticoids is provided by the maintenance of gastric mucosal blood flow, mucus secretion and repair processes as well as the attenuation of pathogenic elements such as enhanced gastric motility and microvascular permeability [Filaretova *et al.* 2004, 2002a, 2002b, 2001b, 1999]. Because the glucocorticoid receptors are expressed ubiquitously it is possible that glucocorticoids may act directly on the cells of local gastric targets as well as using a more general mechanism. According to our results maintenance of glucose and temperature homeostasis as well as systemic blood pressure by glucocorticoids may be a basis for their beneficial action on various gastric targets [Filaretova *et al.* 2006]. This means that glucocorticoids released during activation of the HPA axis may contribute to gastroprotection through their contribution to general body homeostasis. On the other hand, it is also possible that glucocorticoids may have the direct action on local gastric targets [Filaretova *et al.* 2002b; Kanemasa *et al.* 1999].

It is known that both humoral and neuronal factors, such as PGs, nitric oxide (NO), and capsaicin-sensitive afferent neurons, play a pivotal role in the defense against gastric mucosal injury [Takeuchi *et al.* 2001; Holzer, 1998; Wallace, 1997]. 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 compared the effects of the drug-induced inhibition of PG or 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. Subcutaneous (s.c.) indomethacin 35 mg/kg was used as an ulcerogenic stimulus. The glucocorticoid deficiency was caused by adrenalectomy 1 week before the experiment. Two kinds of corticosterone replacement were used in adrenalectomized rats. Indomethacin at a nonulcerogenic dose (5 mg/kg intraperitoneally) or 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 three consecutive doses of 20, 30, and 50 mg/kg [Filaretova *et al.* 2007; Bobryshev *et al.* 2005]. 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, each 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 [Filaretova *et al.* 2007; Bobryshev *et al.* 2005].

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 [Filaretova *et al.* 2007; Bobryshev *et al.* 2005]. These results demonstrate 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 to indomethacin was observed when adrenalectomy was performed together with desensitization of capsaicin-sensitive afferent neurons. Glucocorticoids [Chan *et al.* 2002] and these afferent neurons [Zhou *et al.* 1990] 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 [Filaretova *et al.* 2004, 1999; Holzer, 1998]. 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 deafferented rats is provided by their maintenance of gastric blood flow [Bobryshev *et al.* 2006] and glucose homeostasis [Filaretova *et al.* 2007; Bobryshev *et al.* 2005].

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 [Filaretova *et al.* 2002c] or desensitization of capsaicin-sensitive afferents [Bobryshev *et al.* 2005] 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 cyclo-oxygenase-2 (COX-2) expression [Filaretova *et al.* 2002a].

It has been suggested that 'PGs, NO, and sensory neuropeptides act in concert in the maintenance of mucosal viability' [Whittle *et al.* 1990]. The 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.

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 action of high levels of endogenous glucocorticoids released during acute stress on the stomach is opposite to the harmful actions of exogenous glucocorticoids at pharmacological doses used as a hormonal therapy. NSAIDs as well as other ulcerogenic stimuli, similar to stress, induce an increase in glucocorticoid production that in turn helps the gastric mucosa to resist the harmful actions of

these stimuli. In accordance with our data, an acute elevation of glucocorticoids in the physiological range during stress as well as NSAID and other ulcerogenic actions may itself be gastroprotective. Likewise, a normal basal production of glucocorticoids is also important for the gastric mucosa to resist stress as well other ulcerogenic stimuli. 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 PGs, sulfhydryls, cimetidine or interleukin-1. Although it is established that administration of glucocorticoids to experimental animals can aggravate an acute gastric erosion formation, however in some cases exogenous glucocorticoids may also attenuate an acute gastric erosion formation.

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 a basis for their beneficial influence on gastric mucosal integrity. Furthermore, glucocorticoids 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 suggest that glucocorticoids released during acute activation of the HPA axis are naturally occurring protective factors that play an important role in maintenance of the gastric mucosal integrity.

A perspective: from gastroprotective to proulcerogenic action of glucocorticoids on the gastric mucosa

Thus, in general, glucocorticoid hormones may have dual action on the stomach: a physiological gastroprotective action and a pathological proulcerogenic action. Under physiologic conditions, even in acute stress situations, glucocorticoids have an adaptive effect on the stomach and, therefore, are gastroprotective, while in some situations their action on the gastric mucosa may become proulcerogenic. It is important to understand how physiological gastroprotective action can be transformed to pathological

proulcerogenic effect. We hypothesized that glucocorticoid-induced disturbance of carbohydrate regulation accompanied with the signs of their catabolic effect may be responsible, at least partly, for the transformation. To verify the hypothesis, we investigated the effects of the long-acting glucocorticoid, dexamethasone, on cold-restraint and indomethacin-induced gastric erosion [Filaretova *et al.* 2009a, 2009b]. The results obtained demonstrate that a single injection of dexamethasone at a dose of 1 mg/kg may attenuate or aggravate both cold-restraint- and indomethacin-induced gastric erosion depending on the duration of its action before the onset of the stress or indomethacin, respectively. A short-lasting (1–12 hours) action of dexamethasone attenuated cold-restraint- and indomethacin-induced gastric ulceration. However, a long-lasting (21–24 hours) dexamethasone action resulted in an aggravation of cold-restraint- and indomethacin-induced gastric erosion formation. In our experimental situations, in both ulcerogenic models the transformation of the gastroprotective action of dexamethasone to its proulcerogenic effect occurred 18 hours after the hormone administration, but it is clear that in general this time interval depends on many factors, including the type of glucocorticoid and its dose, and the specificity of the situation. Both short- and long-lasting dexamethasone actions resulted in maintenance of blood glucose levels in fasted, stressed and indomethacin-treated rats. Dexamethasone-induced long-lasting maintenance of blood glucose level accompanied with the signs of catabolic effects preceded the transformation of gastroprotective action of dexamethasone to its proulcerogenic effect. We prolonged our study until the seventh day to verify the questions on how long dexamethasone effects may be continued and whether they are reversible or not. It was found that the dexamethasone-induced proulcerogenic action continued until the fifth day and then, on the seventh day after dexamethasone treatment, it disappeared. The disappearance of dexamethasone-induced maintenance of blood glucose levels preceded disappearance of the signs of catabolic effects and the proulcerogenic action of dexamethasone. The data obtained so far suggest that short-lasting maintenance of blood glucose levels may be responsible for the gastroprotective action of glucocorticoids, while glucocorticoid-induced long-lasting maintenance of blood glucose levels accompanied with the signs of their catabolic effect and glucocorticoid-induced

corticosterone deficiency may be responsible, at least partly, for the transformation of gastroprotective action of glucocorticoids to their proulcerogenic effect [Filaretova *et al.* 2009a, 2009b]. Further investigation of detailed mechanisms underlying the proulcerogenic glucocorticoid action is the task of our future studies. We take into consideration other, additional, possibilities for explanation how physiological gastroprotective action can be transformed to pathological proulcerogenic effect.

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Conflict of interest statement

The author declares no conflict of interest in preparing this article.

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