THE SURPRISING DUAL ACTION OF GLUCOCORTICOIDS

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Glucocorticoid hormones may have dual action on the stomach: physiological gastroprotective and pathological proulcerogenic one. In physiological conditions, even in acute stress situations, glucocorticoids have an adaptive effect on the stomach and, therefore, are gastroprotective. The findings that we review in this article suggest that glucocorticoids released during acute stress are naturally occurring protective factors that play an important role in maintenance of the gastric mucosal integrity.

Keywords: *Hans Selye, stress, the hypothalamic-pituitary-adrenocortical axis, glucocorticoids, non-steroidal anti-inflammatory drugs, gastric erosion, gastroprotection*

A GLÜKOKORTIKOIDOK MEGLEPŐ KETTŐS HATÁSA
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A glükokortikoid hormonok kettős hatást fejtenek ki a gyomorra: élettani gyomorvédő és kóros proulcerogén hatást. Élettani körülmények között, még akut stresszhelyzetben is, a glükokortikoidok adaptív hatást, ezáltal védelmet fejtenek ki a gyomorra. A most áttekintett eredmények azt mutatják, hogy az akut stressz során felszabaduló glükokortikoidok természetesen előforduló védőfaktorok, amelyek fontos szerepet játszanak a gyomornyálkahártya integritásának a fenntartásában.

Kulcsszavak: *Selye János, stressz, hypothalamus-hypophysis-mellékvese tengely, glükokortikoidok, nem szteroid gyulladásgátlók, gyomoreróziók, gyomorvédelem*

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The gastrointestinal tract in general and the stomach in particular is extremely sensitive to a variety of stress situations. Gastric ulcer disease, which is a very common pathology, is regarded as a "stress disease". Despite indubitable advances in elucidation of the pathogenesis of gastric ulceration, there are gaps in our understanding of ulcerogenesis, particularly, the role of key hormonal system of adaptation: the hypothalamic-pituitary-adrenocortical (HPA) axis, and consequently, glucocorticoid hormones.

Glucocorticoids 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 has been considered. Although there is a long-standing debate over whether glucocorticoid therapy by itself leads to peptic ulcer disease in human, it is established that administration of glucocorticoids to experimental animals can result in an acute gastric erosion formation[1]. In the same time, in some cases administration of glucocorticoids to animals can attenuate gastric erosion[2, 3]. It is also known that basal glucocorticoid production contribute to the maintenance of the gastric mucosal integrity. The glucocorticoids may have a permissive role in allowing gastroprotective mechanisms to exert their full potential. A permissive role of glucocorticoids in gastric mucosal protection induced by prostaglandins, sulfhydryls, cimetidine was demonstrated for the first time by Szabo et al[4].

The most controversial question is the question about the action of stress-produced glucocorticoids. For several decades it was generally accepted that glucocorticoids released during stress are ulcerogenic hormones. Main approach used to support

this view 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.

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 performed experiments in rats to clarify the validity of this view. The results obtained do not support the traditional view and suggest that glucocorticoids released during acute activation of the HPA axis are important gastroprotective factors.

Gastroprotective action of glucocorticoids released during acute activation of the HPA axis

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, 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[5, 6].

From the very outset, researchers have focused on the idea that stress-produced 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[5]. Nevertheless for a long time stress-produced glucocorticoids were considered as ulcerogenic hormones.

From the beginning[7], 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. 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 creating a lesion on the hypothalamic paraventricular nucleus, the immunoneutralization of 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 was used in our experiments[7-9].

The data obtained show that the reduction in the stress-induced corticosterone release (by any approaches as stated above), as well as prevention of its actions (by glucocorticoid receptor antagonist), aggravates stress-caused gastric erosion[7-9]. It is suggested that an acute increase in corticosterone during stress protects the gastric mucosa against stress-induced injury.

Further support for the point of view that glucocorticoids released during acute stress are gastroprotective factors came from our results demonstrated that glucocorticoids contribute to gastroprotective effect of preconditioning mild stress. Indeed, we demonstrated that mild stress decreased the gastric ulceration caused by severe stress and this effect was prevented by glucocorticoid deficiency during mild stress[10].

Non-steroidal anti-inflammatory drugs (NSAIDs) as well as stressful lifestyle make significant contributions to gastric ulcer disease. We demonstrated that 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[11-13]. It has been considered previously that combined NSAIDs treatment with therapeutic doses of glucocorticoid increases the risk of gastric ulceration. The results obtained in our studies[11-13] suggest that the increased risk of adverse gastric reactions should be considered when NSAIDs are used in patients with impaired glucocorticoid production.

According to our data gastroprotective effect 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[14, 15]. In addition, glucocorticoids released during acute 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[14, 15]. Furthermore, glucocorticoids exert a compensatory gastroprotective role in the case of impaired gastroprotective mechanisms provided by prostaglandins, nitric oxide, and capsaicin-sensitive sensory neurons[16]. These findings support idea that gastroprotective action of glucocorticoids is an essential element of their general adaptive action.

Thus, the results obtained in our studies 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.

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 gastric mucosa is opposite to the deleterious actions of exogenous glucocorticoids at pharmacological doses used as a hormonal therapy.

Thus, in general glucocorticoid hormones may have dual action on the stomach: physiological gastroprotective and pathological proulcerogenic one. In physiological 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. This question is under our consideration [Filaretova *et al*. 2009].

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