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REVIEW ARTICLE

# The Realization of the Brain-Gut Interactions with Corticotropin-Releasing Factor and Glucocorticoids

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**Abstract:** ***Background***: The brain and the gut interact bi-directionally through the brain-gut axis. The interaction is mediated by the autonomic nervous system and the hypothalamic-pituitary-adrenocortical (HPA) system. The first brilliant demonstration of the brain-gut interactions was the cephalic phase of gastric and pancreatic secretion discovered by Ivan Pavlov, the first physiologist who was awarded the Nobel Prize for Physiology or Medicine in 1904. This review aims to identify the HPA system as a key hormonal branch of the brain-gut axis in stress.

***Methods***: We first outlined main components of the brain-gut axis and then focused on the HPA system as a key hormonal branch of the brain-gut axis in stress. We undertook a structured search of bibliographic databases for peer-reviewed research literature using a focused review question.

***Results***: Seventy-one articles were included in the review, the eleventh of them were articles of Filaretova L. and co-authors. We will discuss in our articles how an endocrinological approach to gastroenterological field can advance our understanding of the HPA axis role in regulation of gastric mucosal integrity and uncover new findings. According to these findings activation of the HPA system is gastroprotective component of the brain-gut axis in stress but not ulcerogenic one as it was generally accepted. Corticotropin-releasing factor (CRF) and glucocorticoids are important natural players provided gastroprotection. The results suggest that an initial action of endogenous glucocorticoids, including stress- and CRF-produced ones, as well as exogenous glucocorticoids, even used at pharmacological doses, is physiological gastroprotective. Prolongation of the hormonal action may lead to the transformation of gastroprotective hormonal effect to proulcerogenic one.

***Conclusion***: The findings of this review demonstrate that corticotropin-releasing factor and glucocorticoids contribute to the realization of the brain-gut interactions and that activation of the HPA system is gastroprotective component of this interaction in stress.

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## 1. THE BRAIN-GUT INTERACTIONS

The brain and the gut interact bi-directionally through the brain-gut axis. Realization of the interactions occurs through neuronal pathways *via* the efferent and afferent components of the parasympathetic and sympathetic nervous system, hormonal pathway including the hypothalamic-pituitary-adrenocortical (HPA) axis as well as components of the immune system and the microbiota [1-4].

The first brilliant demonstration of the brain-gut interactions was the cephalic phase of gastric and pancreatic secretion followed later by further brilliant demonstration, namely a conditional reflex, both discovered by Ivan Pavlov, the first physiologist who was awarded the Nobel Prize for Physiology or Medicine in 1904 [5, 6]. Pavlov developed the surgical method of the «chronic» experiment with extensive use of fistulas which enabled him to see the normal secretion of digestion. Pavlov's seminal findings showed that the sight, smell or taste of food in dogs with chronic esophagostomy induces a vagal-dependent gastric acid secretion. These observations established the concept of the cephalic phase of digestion [7, 8].

Thus, the interaction between the brain and the stomach influences gastric function. At the same time, the stomach has effects on the brain too [9]. The disturbances in the links between the stomach and the brain may result in wide-spread functional gastrointestinal disorders [9].

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It has been emerged over the past decade that the gut microbiota influences the brain-gut axis [3, 10]. The gut microbiota may effect both brain development and future behavior [11]. Modulation of the gut microbiota is considered as a successful approach for treatment stress-related disorders of the central nervous system [12].

The HPA axis plays main endocrine role in the brain-gut interaction. A central mediator of stress response corticotropin-releasing factor (CRF) is a main stimulator of the HPA axis. In addition to regulation of the HPA axis activity, CRF also participate in regulation of inflammation, visceral hypersensitivity, gut motility and permeability [4]. Yvette Taché and her group for the first time established that CRF contributes to gut function disturbances caused by stress [4, 13, 14].

## 2. THE HPA AXIS AS A HORMONAL BRANCH OF THE BRAIN-GUT INTERACTIONS IN STRESS

Stress may alter the brain-gut interactions leading to the development of gastrointestinal disorders including inflammatory bowel disease, functional gastrointestinal diseases, peptic ulcer. The major pathological influences of stress on the gastrointestinal tract consist in changes in gastrointestinal motility and secretion, increase in intestinal permeability and visceral perception, decrease in mucosal blood flow [15]. Stress may also cause negative alterations in the intestinal microbiota [15].

Activation of the HPA axis is the main distinctive feature of stress reaction. This discovery belongs to Hans Selye who is considered as the founder of stress concept. Before Selye's historical article published in 1936 [16], only the release of catecholamines was considered as the neuroendocrine response to nonspecific injury [17]. Hans Selye discovered the crucial role of the hypophysis-adrenal cortex axis in the stress response [18]. He also introduced the names of glucocorticoids (for the endhormones of the HPA axis) and mineralocorticoids, moreover, discovered the anti- and pro-inflammatory properties, respectively, of these steroids in animal models [19, 20].

One of stress-related pathology is a form of gastric ulceration, called "stress ulcer" [21]. The first stress-induced gastric ulcer in rats were described by Hans Selye [16], he also characterized the first human "stress ulcer" during the air-raids in London during World War II [19].

Hans Selye attracted an attention to relation between stress-induced glucocorticoids and gastric ulcer when he described the typical triad of the alarm reaction: gastric ulceration, thymolymphatic atrophy, and adrenal hypertrophy [16]. These three types of changes formed a definite syndrome, because they were closely interdependent in some way: when Selye injected only a small amount of the extract which caused the changes, all of the changes were slight, but when he injected much extract, they were all very pronounced. Hans Selye called the entire non-specific response the general adaptation syndrome [16, 22] and later the stress syndrome. He found that the pituitary adrenocorticotrophic hormone (ACTH) is responsible for adrenal hypertrophy in stress and further raised the question about an existence in the hypothalamus the first mediator of the stress response, *i.e*. CRF [23]. The precise role of hypothalamus as a bridge between the brain and the endocrine (the hypophysis-adrenal cortex) system was recognized later. It was partly through the work of A.V. Shally and Selye's former graduate student Roger Guillemin [24] and mainly through Guillemin's former student Willy Vale who isolated CRF and characterized as a 41-amino acid peptide in 1981 [25].

One can say that a discovery of stress tried by Selye, his further findings on a stimulatory role of ACTH in stress-induced adrenal enlargement and his reasonable presumption about an existence in the hypothalamus the first mediator of the stress response CRF [24] resulted in demonstration of the crucial hormonal branch of the brain-gut (the brain-stomach) interactions, namely the HPA axis, in stress.

It was alluring to assume that stress-produced glucocorticoids are a reason of gastric ulcerogenesis in stress. This possibility was also verified by Selye. For this he estimated effects of hypophysectomy and adrenalectomy on stress-induced gastric ulceration. Because according to his results stress-caused gastric injury was not attenuated by these operations leading to gucocorticoid deficiency, it was concluded that stress ulcers depends on not only the pituitary-adrenal axis [26].

Positive correlation between the severity of stress-induced ulceration and corticosterone levels in plasma which was found in some experimental studies in rats was considered as a support of ulcerogenic role of stress-produced glucocorticoids [27, 28]. Another basis for this point of view was related with an extrapolation of the ulcerogenic properties of exogenous glucocorticoids at pharmacological doses in humans and animals [28-39] to the properties of stress-induced glucocorticoids.

Despite the fact that some studies did not confirm ulcerogenic role of endogenous glucocorticoids [40-44] for several decades it has been generally accepted that glucocorticoids produced during stress are ulcerogenic hormones.

### 2.1. Activation of the HPA axis as Gastroprotective Component of the Brain-Gut Interactions in Stress

As this widely accepted view about ulcerogenic role of glucocorticoids produced during stress contradicts their adaptive role [45], we further clarified the question. Our work hypothesis was that stress-produced glucocorticoids are gastroprotective.

#### *2.1.1. Gastroprotective Role of Stress-produced Glucocorticoids*

To check the hypothesis, we studied the effects of the inhibition of stress-induced glucocorticoid levels or the occupation of glucocorticoid receptors by their antagonist RU-38486 on stress-caused gastric erosion in preliminary fasted rats [2, 46-49]. To inhibit stress-induced corticosterone production in rats several various approaches with further appropriate corticosterone replacement were applied.

Dexamethasone implantation into hypothalamus or ACTH antiserum administration inhibited stress-induced increase in corticosterone and provoked the gastric injury

caused by cold-restraint as well as water and immersion-restraint stress. These aggravating effects were prevented by corticosterone replacement that mimicked the stress-induced corticosterone response [48]. Similar results were obtained in a model of pharmacological inhibition of the HPA axis at hypothalamic and pituitary levels by cortisol [2, 46, 47, 49]. This treatment resulted in long-term deficiency of stress-released corticosterone and aggravation of gastric injury caused by cold-restraint as well as water and immersion-restraint stress. Corticosterone replacement again attenuated the harmful effects of cortisol pretreatment on the gastric mucosa during stress [2, 46, 47, 49]. If inhibition of stress-released corticosterone in rats potentiates gastric injury caused by stress it means that corticosterone rise during stress plays gastroprotective but no ulcerogenic role.

This conclusion was strongly supported by our results about contribution of stress-released glucocorticoids to protective effect of preconditioning mild stress against gastric injury caused by severe stress [50]. We demonstrated that a decrease in corticosterone release in response to preconditioning mild 30 min cold-restraint prevented its protective effect on the gastric erosion caused by severe 3 h cold-restraint stress [50]. The findings together confirm that stress-produced glucocorticoids are gastroprotective homones.

The gastroprotective action of glucocorticoids during stress may be related with their beneficial effect on the gastric blood flow. Blood supply is a critical component of gastroprotection and gastric injury [51]. The cardiovasular parameters, including blood pressure are the main determinants of the blood supply, and are in direct relationship with the development of ulceration [52]. It is known that stress-caused decrease in gastric mucosal blood flow leads to mucosal ischemia and further development of the gastric injury in stressed rats [52]. Applying *in vivo* microscopy for the direct visualization of gastric microcirculation, we found that a decrease in corticosterone response to water immersion-restraint stress resulted in an increase in gastric microvascular permeability, a decrease in blood pressure and in blood flow velocity in mucosal micro-vessels, and as a result aggravation of the gastric erosion in rats. Corticosterone replacement prevented all these effects [53, 54]. The results suggest that gastroprotective actions of glucocorticoids during stress may be provided by the maintenance of gastric mucosal blood flow. In turn, this beneficial effect of stress-produced glucocorticoids on the gastric mucosal blood supply may be provided by the maintenance of arterial blood pressure [53, 54].

The glucocorticoid receptors are ligand-inducible transcription factors that ubiquitously expressed in most tissues in rats [55] including the gastric mucosa [56]. After hormone binding glucocorticoid receptors are rapidly translocate from the cytoplasm into the nucleus [57]. RU-38486 is widely used glucocorticoid receptor antagonist which is bound up with a high affinity to type II glucocorticoid receptors [58, 59]. Glucocorticoid receptors are predominantly occupied by RU-38486 comparing glucocorticoids in the simultaneous their presence [60].

RU-38486 was used in our studies as a tool to verify the role of stress-induced corticosterone increase in gastric ulceration and also to investigate gastroprotective mechanisms of glucocorticoids. We found that pretreatment with RU-38486 significantly potentiated stress-induced gastric erosion [48]. These data obtained confirm the gastroprotective role of stress-released glucocorticoids. The findings also suggest that this protective action of glucocorticoids on the gastric mucosa may be provided through genomic mechanism.

Beneficial action of glucocorticoids on the gastric mucosa may be provided through multiple targets. Glucocorticoids maintain the gastric mucosal blood flow, mucus secretion and processes of gastric mucosa reparation as well as attenuate enhanced microvascular permeability and gastric motility [53, 54]. Glucocorticoids may act directly on the gastric mucosal components and also indirectly through various links of general body homeostasis. We demonstrated that maintenance of systemic blood pressure as well as glucose and temperature homeostasis by glucocorticoids may be a basis for their gastroprotective action [2]. These results suggest that stress-produced glucocorticoids may contribute to gastroprotection through their contribution to general body homeostasis.

Thus, our findings suggest that stress-produced gluco-corticoids are gastroprotective but not ulcerogenic hormones. The action of natural stress-released glucocorticoids on the gastric mucosa is opposite to ulcerogenic effect of exogenous glucocorticoids used at pharmacological doses.

#### *2.1.2. Gastroprotective Role of CRF: Involvement of Glucocorticoids*

One of the key mediators in the bodily response to various stressors and the brain-gut interactions is the CRF [4]. CRF is synthesized in the hypothalamic paraventricular nucleus and exert a crucial role in the maintenance homeostasis through the HPA axis stimulation [8, 61, 62]. Type 1 CRF receptors on pituitary corticotrophs are the primary receptors mediating an increase in ACTH levels in stress [61]. Additionally CRF may act independently of the HPA activation [23].

It is recognized that activation of the CRF signaling system is involved in stress-related disorders, including gastrointestinal disorders [4, 23]. At the same time, it is known that the CRF system activation is also a pivotal physiological reaction. The results that we will discuss here support physiological, gastroprotective, action of CRF.

There are findings demonstrating protective influence of endogenous CRF on restraint-produced gastric mucosal injury [63] and protective effect of exogenous CRF on the gastric injury caused by cold-restraint [13, 64, 65] or water-immersion restraint [66, 67] in rats. In these studies gastroprotective effects were demonstrated after the central injections. The action of CRF after its peripheral administration on the gastric mucosa remained unclear.

Thus, exogenous CRF induces an increase in blood glucocorticoid levels and at least in some situation may also exert protective influence against stress-induced gastric mucosal injury. It would seem logical that the question of the role of CRF-induced glucocorticoids in stress-caused

gastroprotection will appear to study. However, well-deserved interest in the matter was absent, probably due to wide-spread view about ulcerogenic role of stress-released glucocorticoids.

The results of our studies about gastroprotective role of stress-produced glucocorticoids were the basis for us to investigate the question about a contribution of CRF-released glucocorticoids to gastroprotective effect of CRF. Because the influence of peripheral CRF on the gastric mucosa remained unclear we used intraperitoneal administration of CRF. The peripheral administration of CRF (at the dose 1.25 mkg/kg, 0.5 h before onset of 3-h cold-restraint stress) rapidly and markedly increased plasma corticosterone level before the stress and decreased stress-induced gastric ulceration in control rats. CRF-induced increase in corticosterone level allowed us to suggest that this acute CRF-induced corticosterone may contribute to gastroprotective action of exogenous CRF. To verify this suggestion two approaches were used: pretreatment of rats with metyrapone, the inhibitor of glucocorticoid synthesis, and pretreatment with RU-38486, the glucocorticoid receptors antagonist. We used metyrapone to decrease glucocorticoid production because of its short-lasting inhibiting effect [68]. Metyrapone administration resulted in a fast decrease of corticosterone response to CRF and prevention of its gastroprptective action. The gastroprotective effect of CRF was also prevented by the pretreatment of rats with RU-38486. The results obtained suggest that CRF-induced glucocorticoids contribute to gastroprotective action of CRF [69]. The findings further support the idea about gastroprotective role of stress-produced glucocorticoids.

## 3. CONCLUSIONS AND PERSPECTIVES

The findings discussed here improve understanding of role of the HPA system as important hormonal branch of the brain-gut interactions. According to the findings activation of the HPA system is gastroprotective component of the brain-gut axis in stress but not ulcerogenic one as it was widely accepted for several decades. Our results suggest that an initial action of endogenous glucocorticoids, including stress-produced ones, as well as exogenous glucocorticoids, even used at pharmacological doses, is physiological gastroprotective. Prolongation of the hormonal action, even after single glucocorticoid injection, may lead to the transformation of gastroprotective hormonal effect to proulcerogenic one [70]. It is critically important to understand the mechanisms underlying the transformation to develop approaches for its prevention.

Recent results suggest that there is crosstalk between the components of the brain-gut interaction such as the HPA system and the vagus nerve [1]. There is a balance between the parasympathetic nervous system and the HPA axis under physiological conditions which is destroyed in Crohn's disease and an inflammatory bowel disease patients [71]. Further studies evaluating the crosstalk between the HPA axis and the autonomic nervous system are needed for understanding functioning of the brain-gut axis in health and disease.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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