IASGO, ICUR & KSGC JOINED SYMPOSIUM
March 22~24, 2018
Grand Hilton Seoul, Seoul, Korea

STRESS:
EVERY CLOUD HAS A SILVER LINING

Ludmila Filaretova

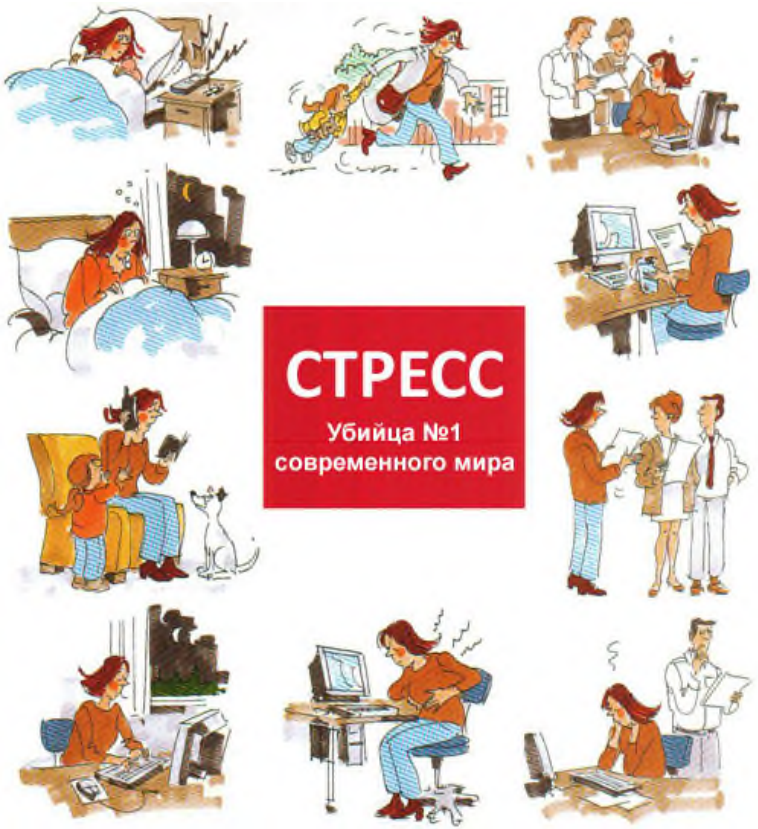
Pavlov Institute of Physiology
Russian Academy of Sciences
St.Petersburg, Russia

“Stress in health and disease is medically, sociologically, and philosophically the most meaningful subject for humanity that I can think of”.

Hans Selye

Stress is a “murderer N1”

“Stress is the salt of life”



“Total elimination of stress – would be equivalent to death”

“We must not suppress stress in all its forms, but diminish distress and facilitate eustress”

H. Selye, 1976

distress

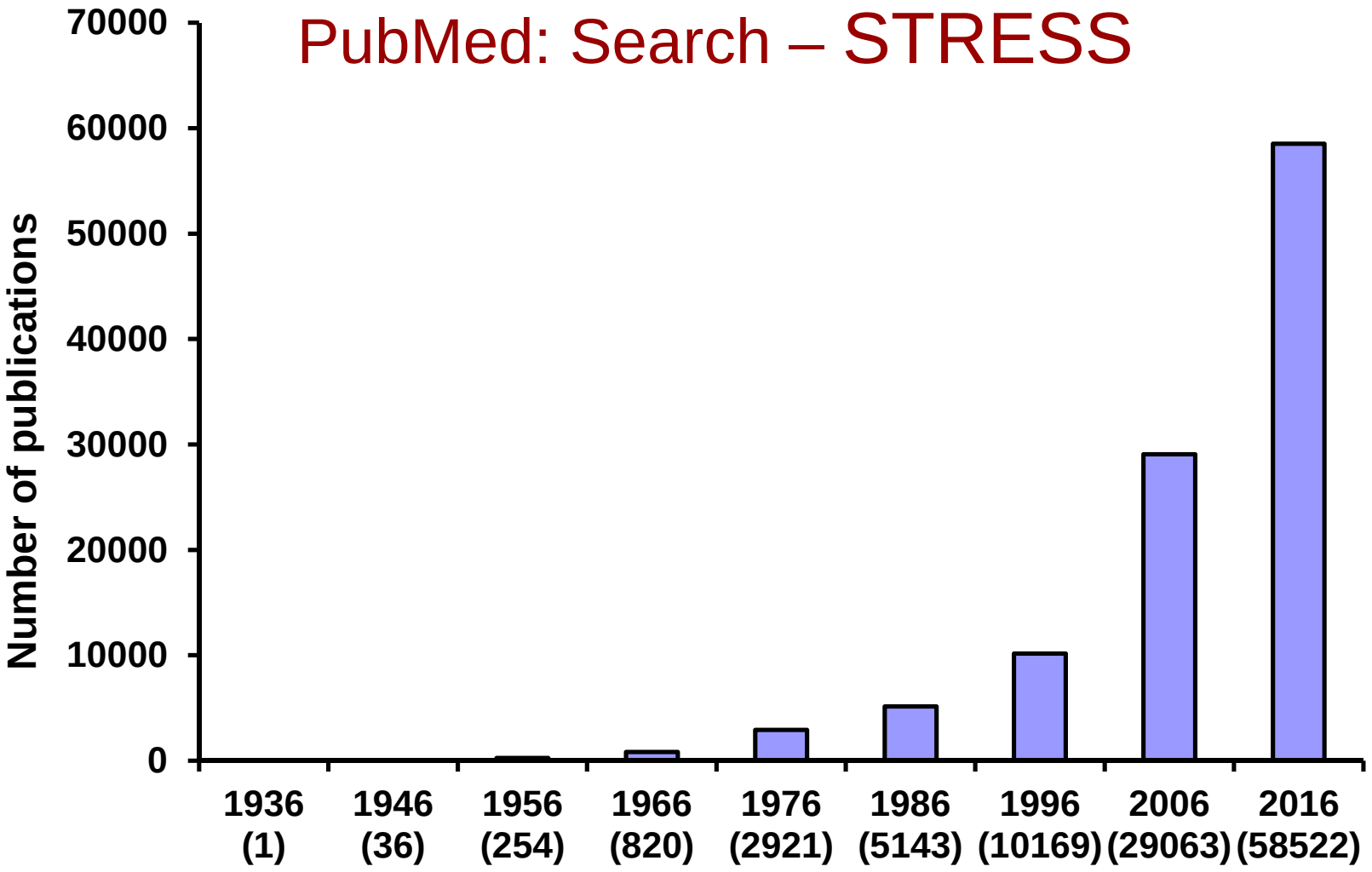
eustress

Stress as a source of a good health

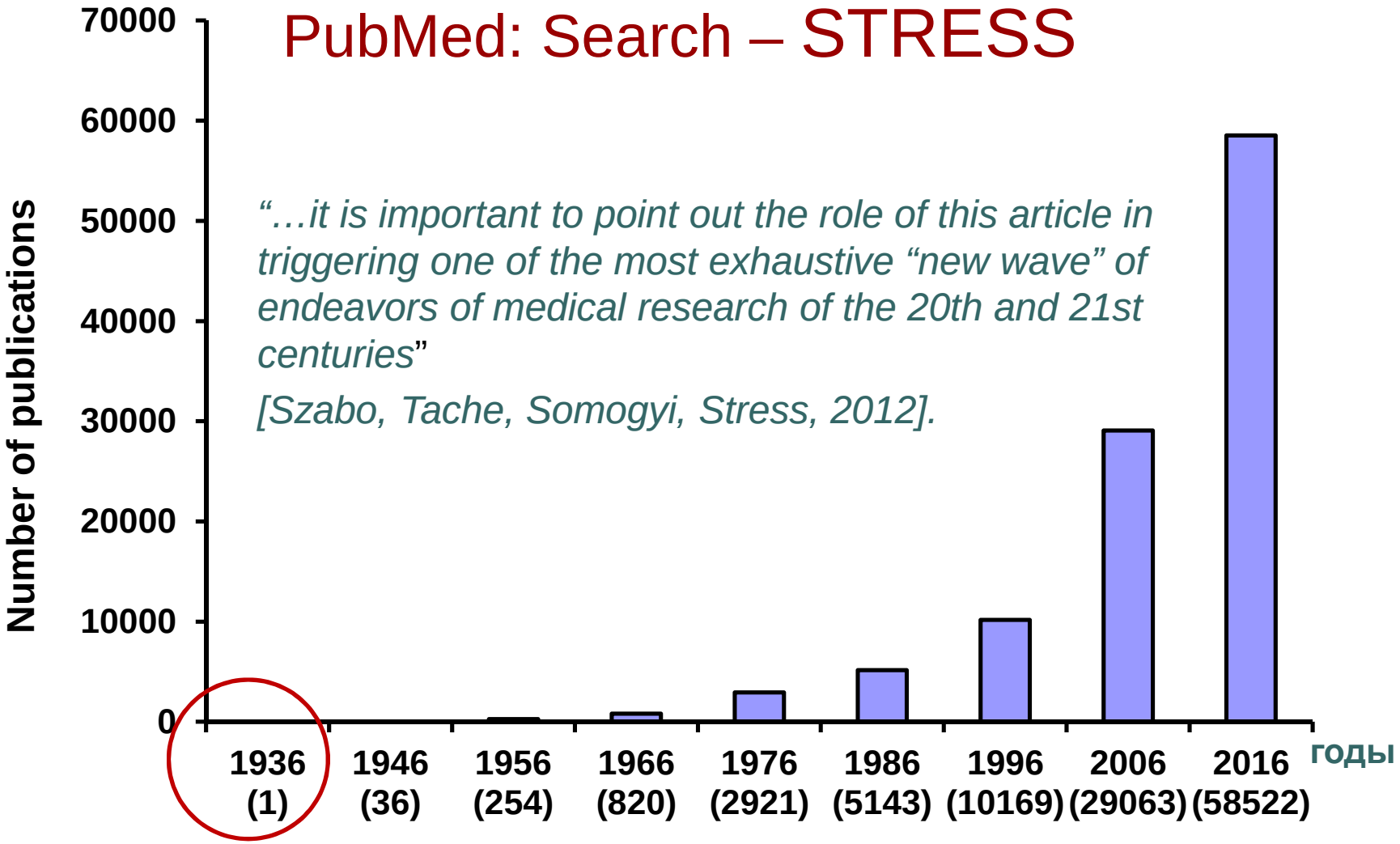
Stress as a cause of the disease are well known. Stress as a source of a good health, the notion is unusual, however, stress research in this aspect is necessary for medicine.

The stress reaction coordinates the mobilization of the body's defenses helping it to overcome problems that arise. The current active study of preconditioning phenomenon supports the conclusion that stress can increase adaptive capabilities of the body.

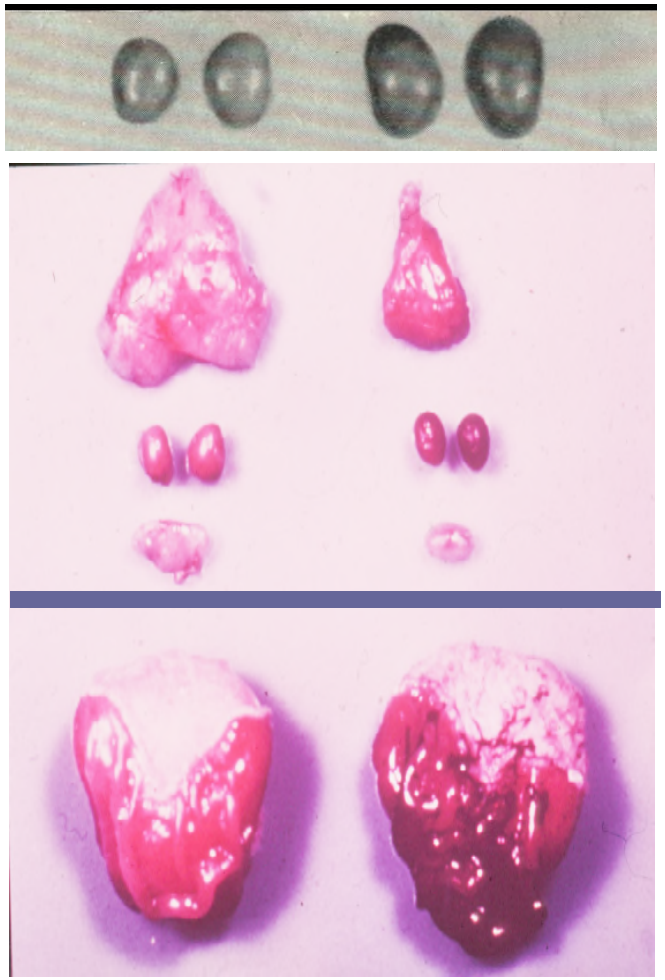
Understanding the significance of stress for health, good and bad, contributes to the progressive development of the field of fundamental research related to various aspects of the stress problem, and, accordingly, to the increase in the number of scientific publications.



Selye H. Syndrom produced by diverse nocuous agents
Nature 138:32, 1936



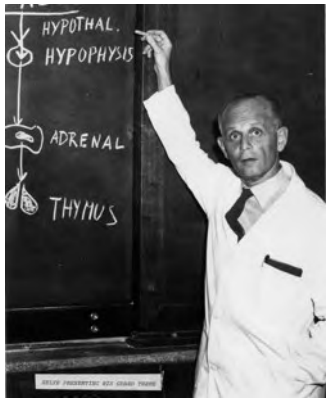
Selye H. Syndrom produced by diverse nocuous agents (Синдром, вызываемый различными повреждающими агентами). Nature 138:32, 1936



“STRESS TRIAD”

- Thymolymphatic atrophy
- **Adrenal hypertrophy**
- **Gastric ulceration**

“general alarm reaction of the organism”



Activation of the HPA axis belongs to the main characteristics of stress

Stressor

⇓

Hypothalamus

⇓ **CRF**
(CRF1-R)

Pituitary

⇓ **ACTH**

Adrenals

Glucocorticoids

Selye H. Syndrome produced by diverse nocuous agents. Nature 138:32, 1936

"STRESS TRIAD"

- Thymolymphatic atrophy
- **Adrenal hypertrophy**
- **Gastric ulceration**

Stress is a source of a good health

The fact that the disturbance of the normal stress reaction by the elimination of the HPA axis's functioning leads to negative effects on the body such as the development and aggravation of diseases proves that stress plays a leading role in maintaining the physical health of the body.

We plan to demonstrate this on the base of the results of our studies related with investigation of interrelations between stress-induced activation of the HPA axis and gastric ulcer diseases.

Role of stress-produced glucocorticoids in stress-caused gastric ulceration

Stress

The HPA axis

Gastric ulceration

Hypothalamus

⇓ CRF

Pituitary

⇓ *ACTH*

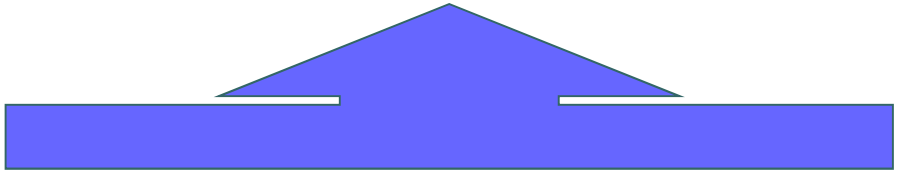
Adrenals

Glucocorticoids ⟶ **?**

Ulcerogenic or Gastroprotective

Stress-produced glucocorticoids are ulcerogenic hormones

Activation of the HPA axis is ulcerogenic component of stress

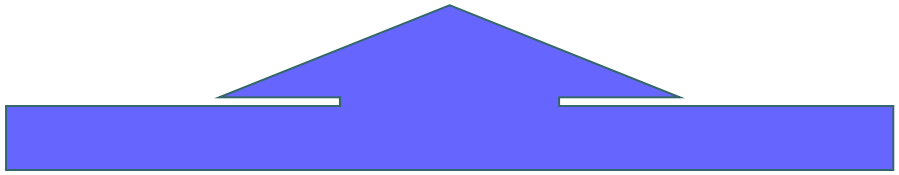


BACKGROUND

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.

Stress-produced glucocorticoids are gastroprotective hormones

Activation of the HPA axis is gastroprotective component of stress



BACKGROUND

Brain Research, 342 (1985) 135–140
Elsevier

BRE 10972

Role of the Paraventricular and Ventromedial Hypothalamic Nuclear Areas in the Regulation of the Pituitary–Adrenocortical System

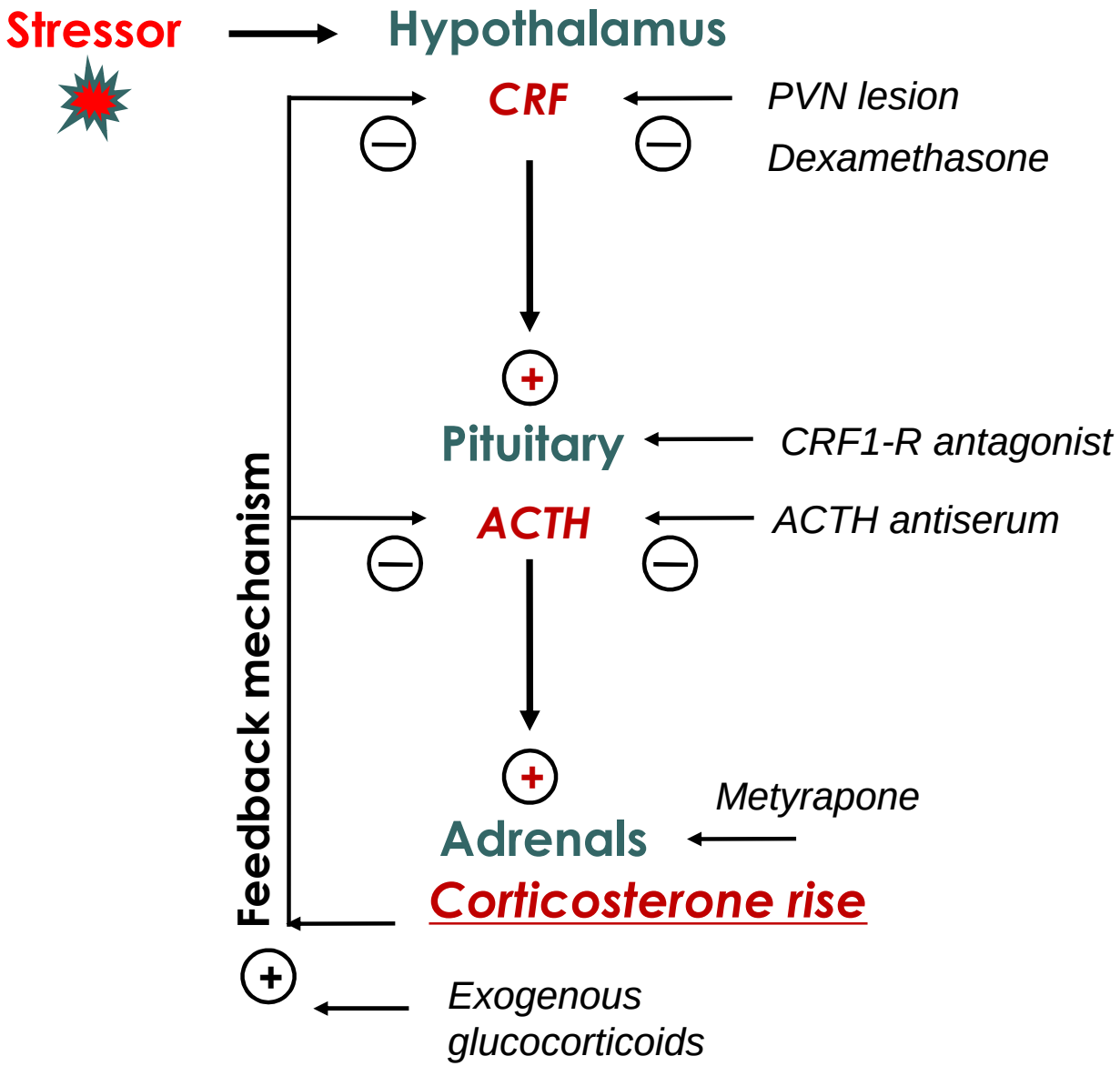
A. A. FILARETOV and L. P. FILARETOVA

Laboratory of Experimental Endocrinology, I.P. Pavlov Institute of Physiology, Academy of Sciences of the U.S.S.R., 199164 Leningrad (U.S.S.R.)

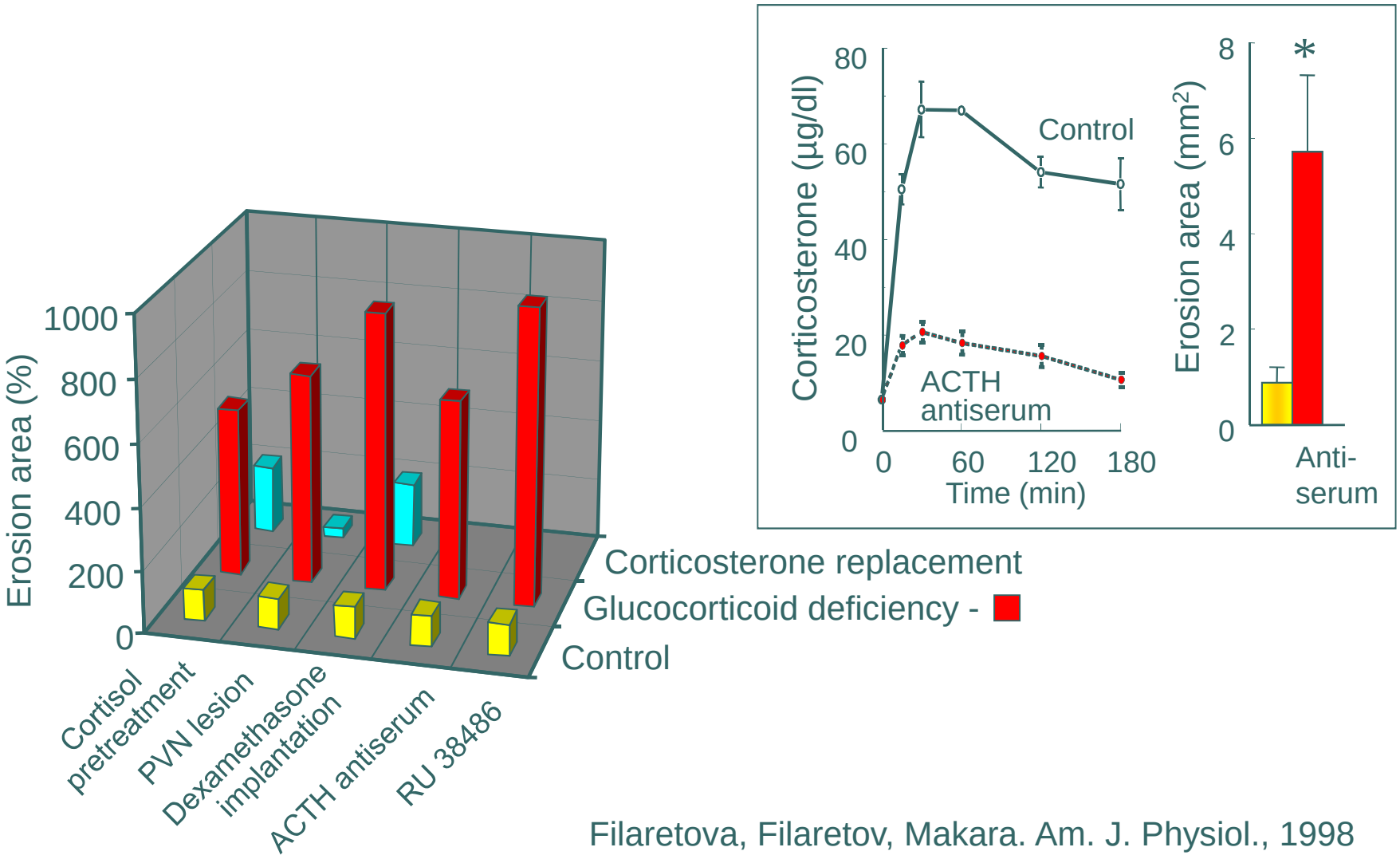
(Accepted December 4th, 1984)

"Endocrinological view"

To create glucocorticoid deficiency



Effect of glucocorticoid deficiency on stress-induced ulceration



Filaretova, Filaretov, Makara. Am. J. Physiol., 1998

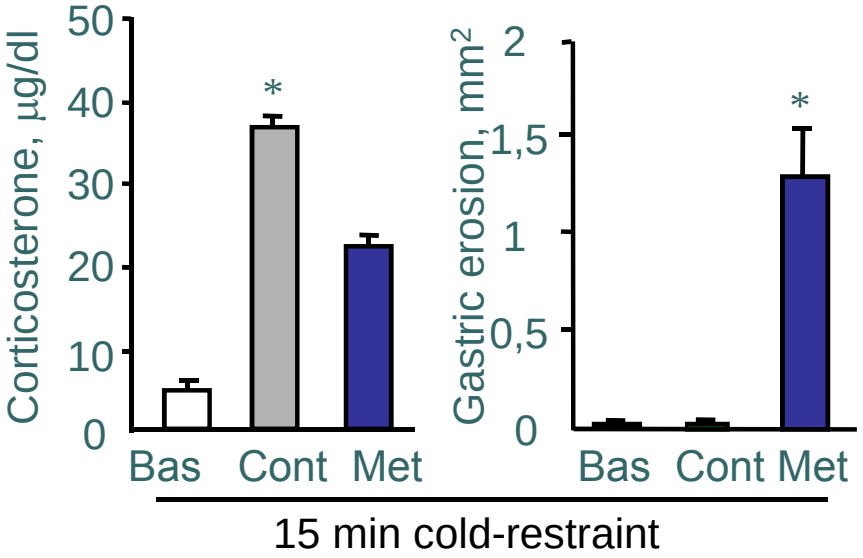
Effect of glucocorticoid deficiency on development of stress-induced ulceration

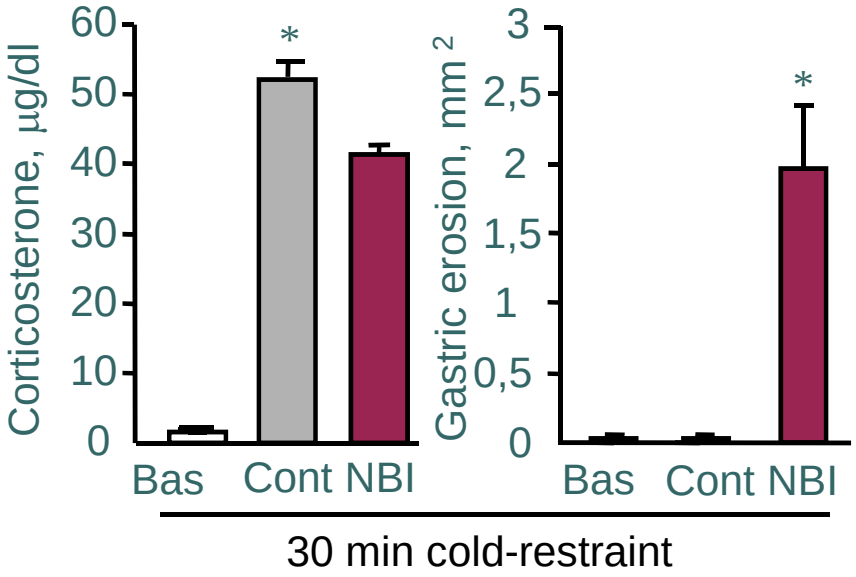
Control (Cont)

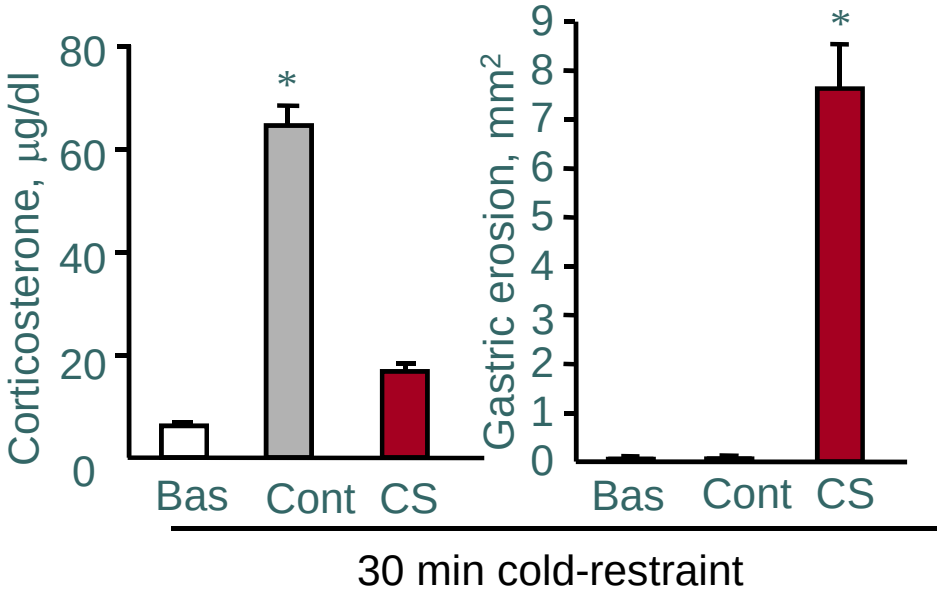
Metyrapone (Met, 30 mg/kg, i.p)

NBI 27914 (NBI, 10 mg/kg, i.p)

Cortisol (CS, 300 mg/kg, i.p)







Filaretova et al., Clinical Neurosci, 2016

Gastroprotective effect of preconditioning stress: the role of glucocorticoids

- Preconditioning mild stress may attenuate the development and aggravation of gastric injury caused by severe stress.

- Preconditioning mild stress induces an increase in glucocorticoid production.

- However, it remained unknown whether glucocorticoids released in response to preconditioning mild stress contribute to its gastroprotective effect.

Gastroprotective effect of preconditioning stress

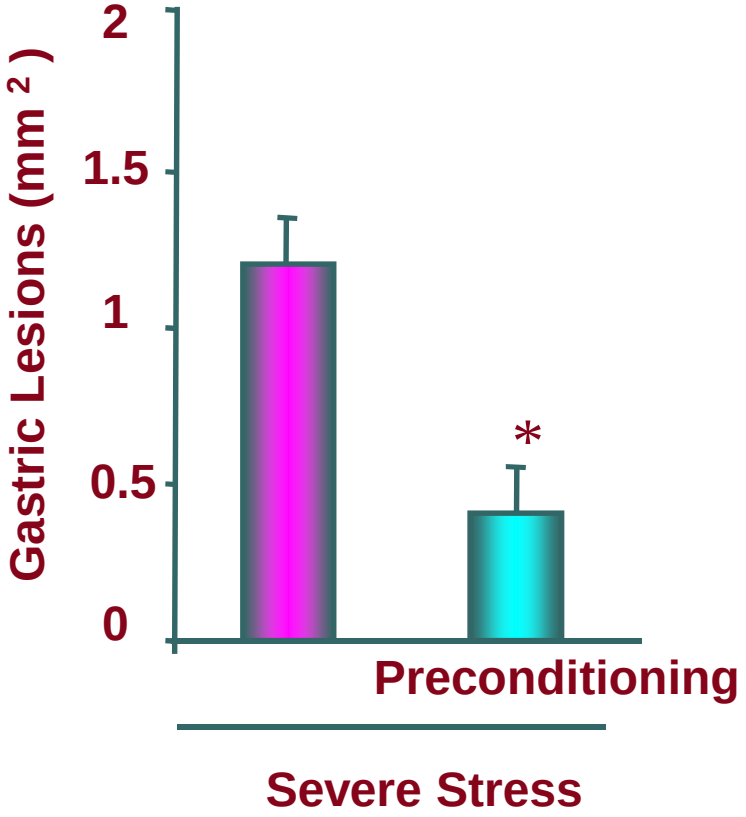
Experimental design

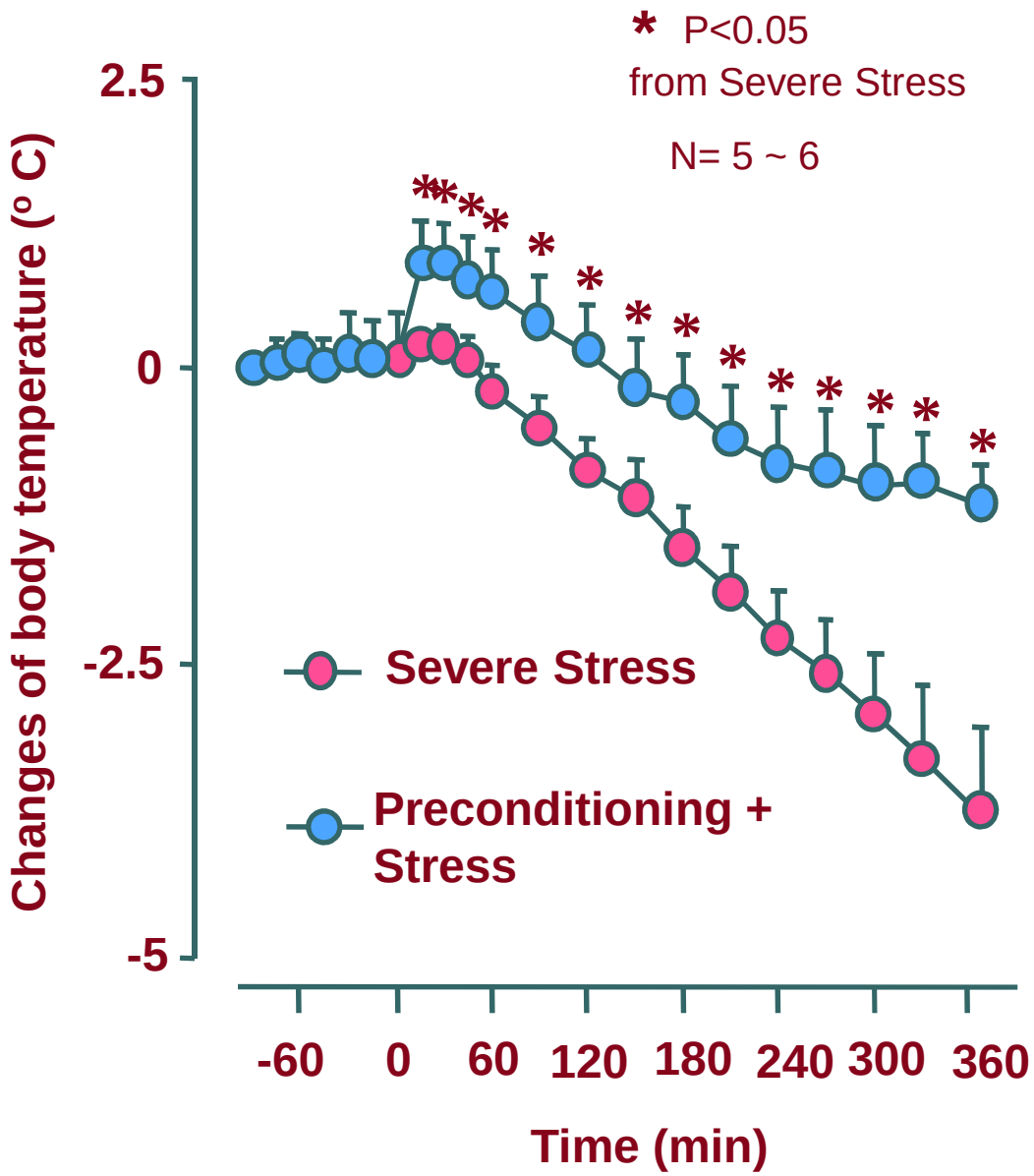
Mild stressor **Ulcerogenic severe stressor**

Rats were exposed to severe stress (Cold-Restraint at 10° C for 6 h) with preconditioning mild stress (Cold-Restraint at 10° C for 30 min and restraint at room temperature for 60 min) or without mild stress.

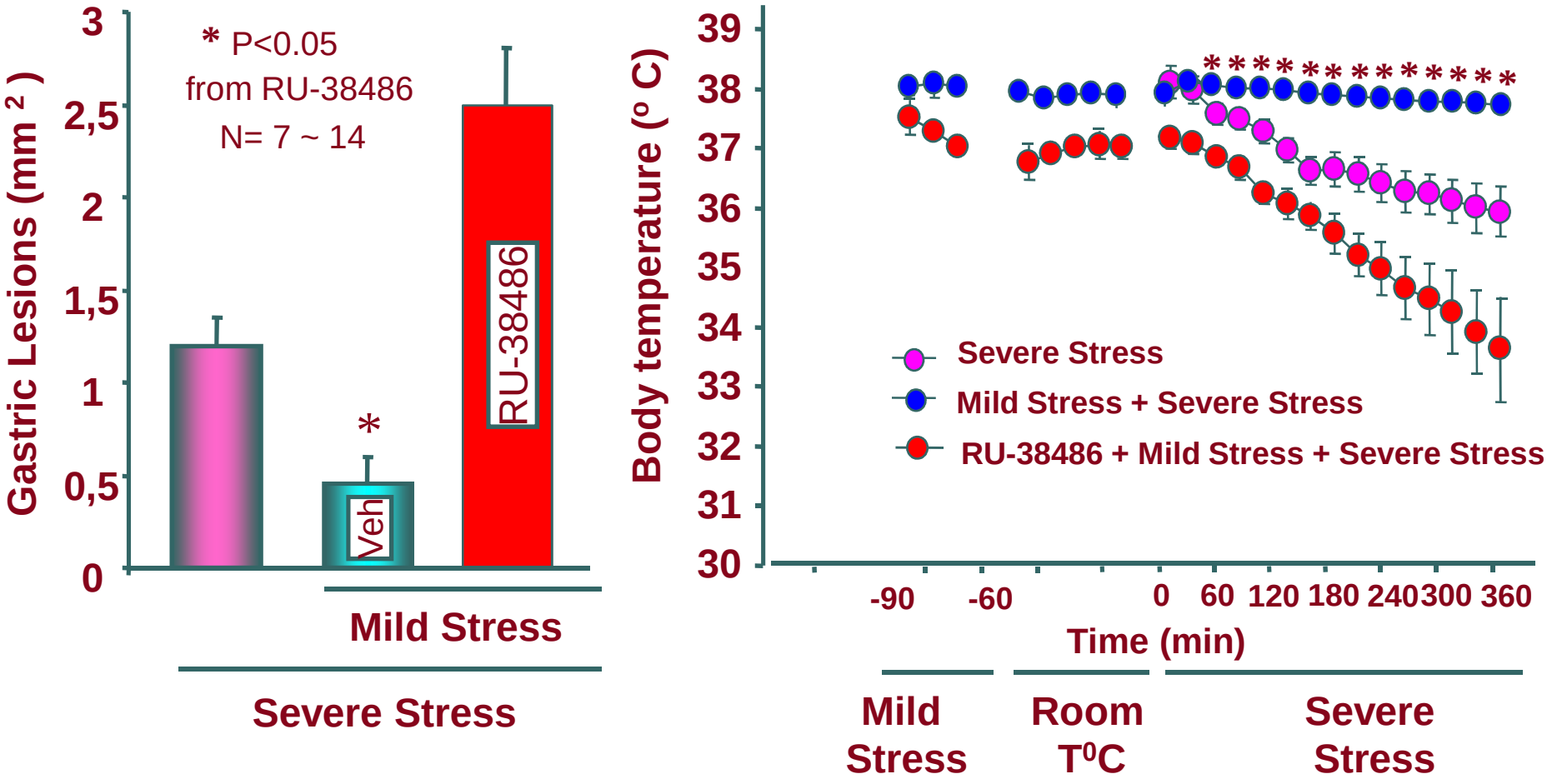
Tanaka A, Hatazawa R, Takahira Y, Izumi N, Filaretova L, Takeuchi K. Dig Dis Sci. 2007

Effects of preconditioning stress on gastric erosion and lowering of body temperature induced by Cold-Restraint





Glucocorticoid receptor antagonist RU38486 prevents the beneficial effects of mild stress on gastric erosions and lowering of body temperature caused by severe stress

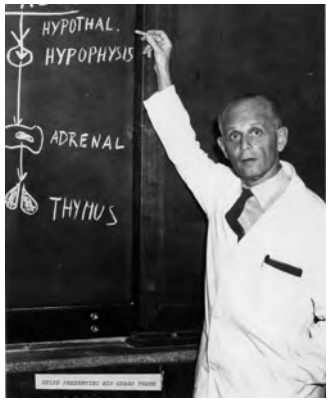


Filaretova LP, Bagaeva TR, Amagase K, Takeuchi K. Ann NY Acad Sci., 2008

CONCLUSIONS

- Glucocorticoids released during preconditioning mild stress contribute to the protective effect of this stress on gastric mucosa against cold-restraint stress-induced gastric lesions.

- The effect is functionally associated with prevention of lowering of glucose levels and body temperature.



Corticotropin-Releasing Factor (CRF) is a central mediator of stress response

Stressor

↓

Hypothalamus

↓ **CRF**

(CRF1-R)

Pituitary

↓ **ACTH**

Adrenals

Glucocorticoids

The stress response involves the activation of two CRF receptors types 1 and 2 (CRF1 and CRF2).

The pituitary CRF1 receptors represent the primary receptors to activate the HPA axis.

CRF also exerts a number of biological actions independently of the HPA axis stimulation through interaction with CRF2 receptors.

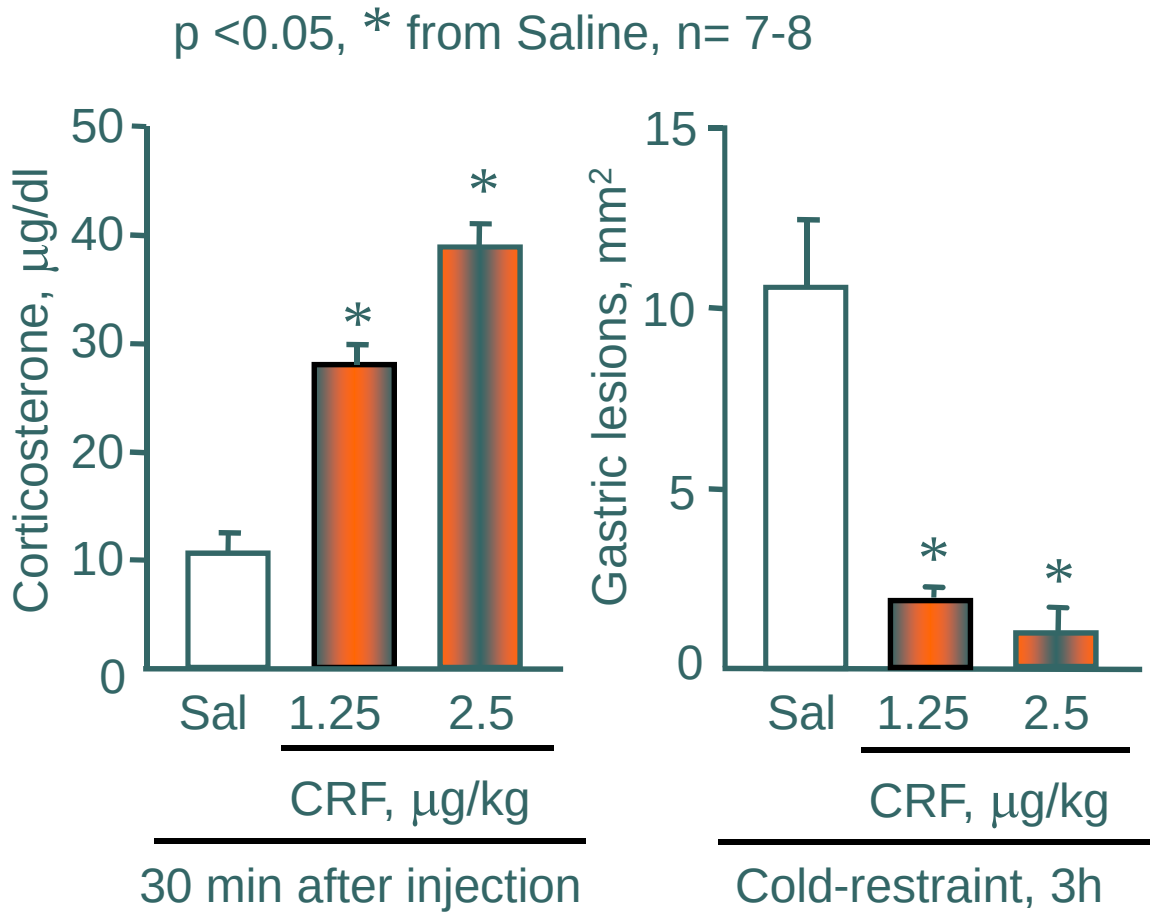
CRF and Gastroprotection

Exogenous CRF induces an increase in glucocorticoid production and may protect the gastric mucosa against stress-induced injury.

The gastroprotective action of exogenous CRF:
3-4 h Cold-restraint
Gunion, Kauffman, Tache, 1990;
Ray, Henke, Gulati, Sen, 1993;
Wang, Cardin, Martinez, Tache, 1996;
2-4 h Water-restraint
Bakker, Bogsness, Murison, 1990;
Shibasaki et al., 1990;
The gastroprotective action of endogenous CRF:
Kawakubo and Tache, 1999

Whether CRF may protect the gastric mucosa against injury through involvement glucocorticoids/CRF_1 receptors?

Gastroprotective effect of CRF



Filaretova et al., Cell. and Mol. Neurobiol., 2012

Gastroprotective effect of CRF

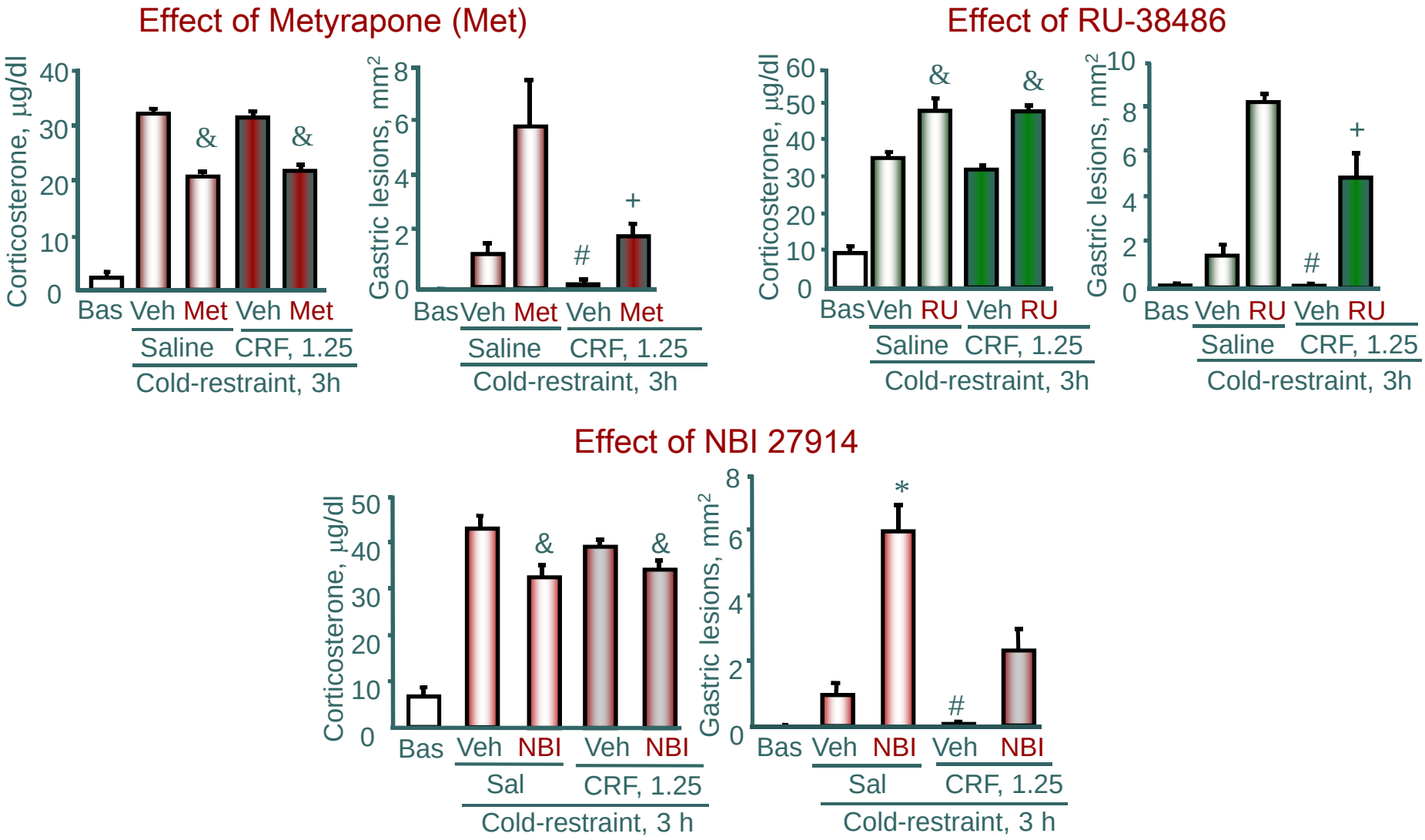
❖ The Role of Glucocorticoids

To verify whether glucocorticoids contribute to gastroprotective effect of exogenous CRF we compared the effects of CRF on the gastric injury:

➢ in rats with normal and deficient corticosterone production; glucocorticoid deficiency was created by inhibition of glucocorticoid synthesis with metyrapone (30 mg/kg, i.p.).

➢ in rats with normal and occupied glucocorticoid receptors by its antagonist RU-38486 (20 mg/kg, i.p.).

Gastroprotective effect of CRF: involvement of glucocorticoids



Filaretova et al., Cell. and Mol. Neurobiol., 2012; Current Neuropharmacol. 2016

Gastroprotective effect of CRF: involvement of glucocorticoids

❖ CRF may protect the gastric mucosa against cold-restraint-induced injury through involvement of glucocorticoids and CRF receptors types 1.

Mechanisms of gastroprotective action of glucocorticoids

Gastroprotective effect of glucocorticoids may be provided by multiple actions, including maintenance of gastric mucosal blood flow, mucus production, repair processes and attenuation of enhanced gastric motility and, microvascular permeability.

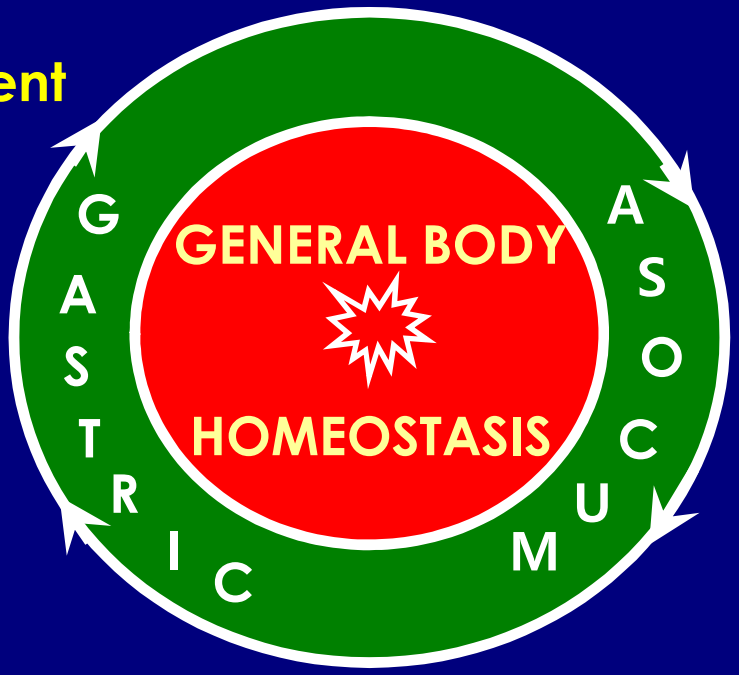
The contribution of glucocorticoids to gastroprotection is tightly related with their contribution to the general body homeostasis. Various parts of the general body homeostasis (blood pressure, blood glucose, body temperature) may be the primary targets of the glucocorticoid action.

Russian J. Physiology 2000-2017;
J. Physiol. Paris, 2001;
Am. J. Physiol., 1998,2002;
Life Sci., 2002;
Ann NY Acad. Sci, 2004;
Inflammopharmacology 2002, 2005-2009;
Auton. Neurosci. 2006;
J. Pharmacol. Sci. 2007;
Ann NY Acad. Sci, 2008'
J. Physiol. Pharmacol. 2009, 2011;
Regul. Peptides, 2010;
Cell Mol Neurobiol. 2012;
Curr Pharm Des. 2017;
Curr Neuropharmacol 2016

Gastroprotective action of glucocorticoid hormones is a essential element of their general adaptive effect

Gastroprotection during NSAID treatment

Compensatory gastroprotection



Gastroprotection during stress

Adaptive gastroprotection/ Preconditioning