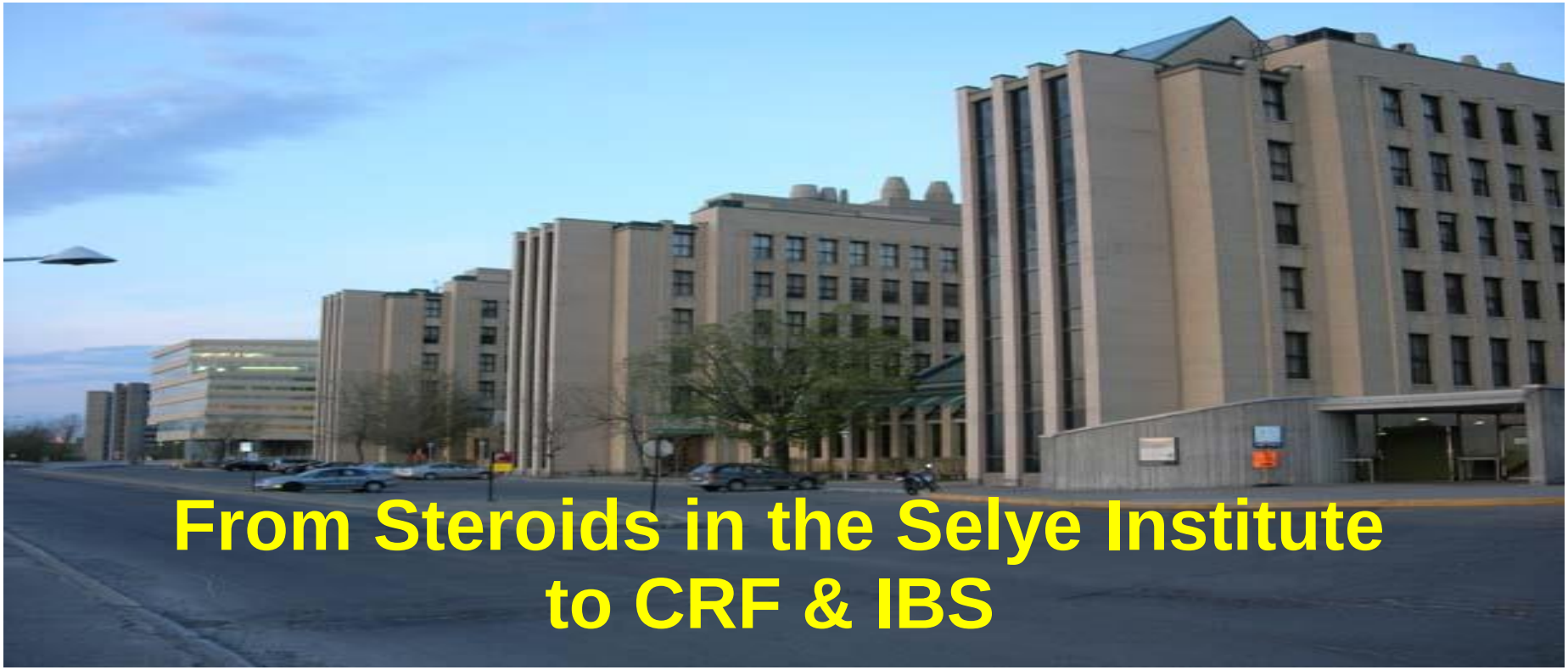
MTA/Hungarian Academy of Sciences, Budapest

Biological Stress is 80 years old-
After the first article of Hans Selye (Nature 1936)



Yvette Taché, PhD

Center for Neurobiology of Stress & CURE: Digestive Diseases Research Center, UCLA, and VA Los Angeles

Catatoxic Steroids and the Modulation of Biological Function and Drug Actions

Selye H, Taché Y, Szabo S. Interruption of pregnancy by various steroids. Fertil Steril. 1971; 22:735-40.

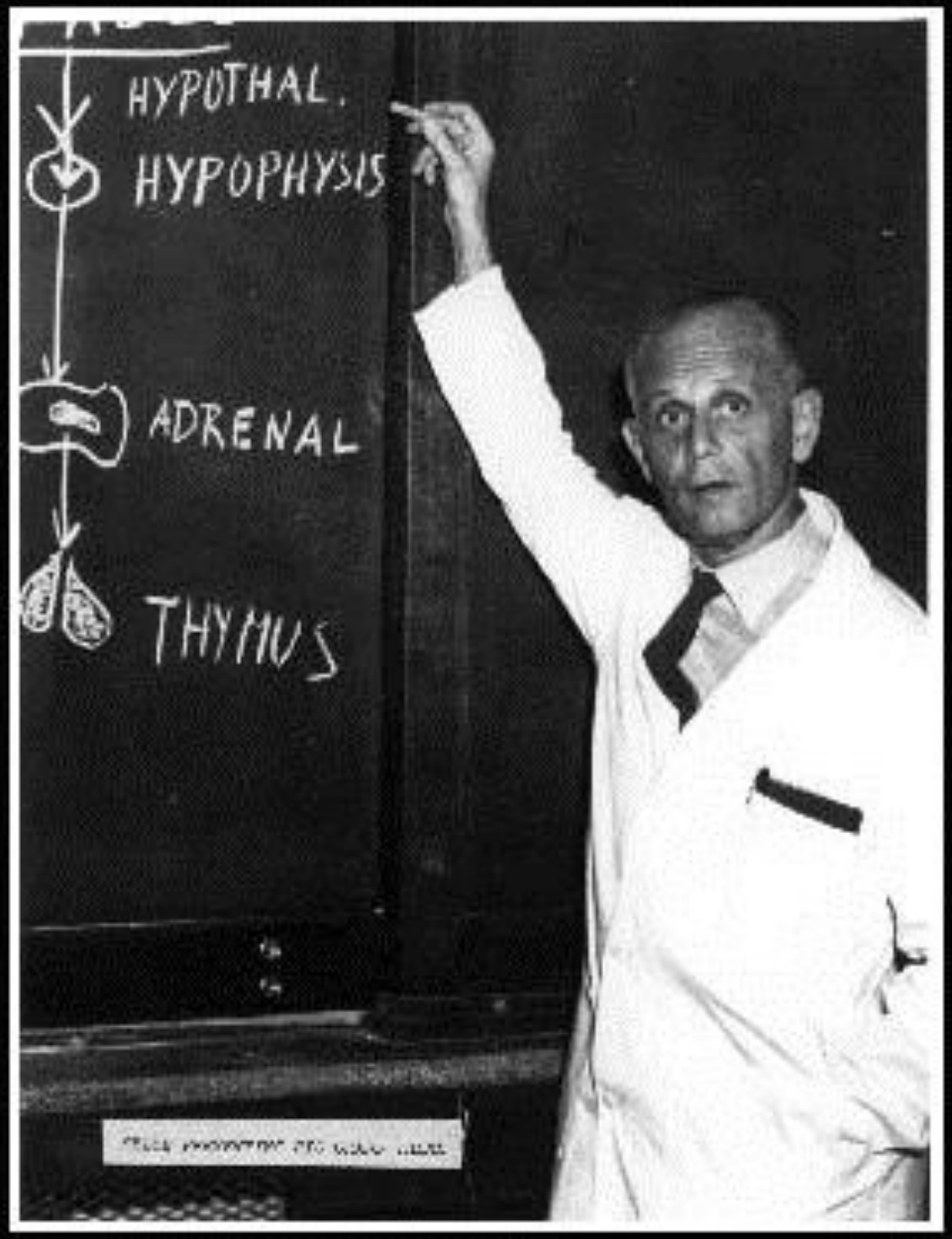
Szabo S, Selye H, Kourounakis P, Taché Y. Comparative studies on the effect of ACTH and pregnenolone-16alpha-carbonitrile (PCN) upon drug response and distribution in rats. Biochem Pharmacol. 1974 39:319-27

Kourounakis P, Selye H, Taché Y. Catatoxic steroids. Adv Steroid Biochem Pharmacol. 1977;6:35-57. Review.

Taché Y, Taché J, Selye H. Inhibition of the effects of alfathesin and other steroid anesthetics by catatoxic steroids in rats. Arzneimittelforschung. 1975;25:1603-6.

Yousuf KARSH:
Photo of Dr. Hans Selye & coworkers.
Universite de Montreal, 1971

HANS SELYE, MD, PhD 1907-1982



Discover in 1936 the concept of STRESS defined as "the non-specific response of the body to any demand."

He first established **the HPA axis, immune system** and the **GUT** at the **center of the stress-reactive syndrome.**

Key initial observations of brain-gut interactions

Taché, Y, Simard P and Collu R. Prevention by bombesin of cold-restraint stress-induced hemorrhagic lesions in rats. Life Sci. 24:1719-26, 1979

Endocrinology lab. Univ. Montreal, Montreal, Canada

Table 1. The 14-aa peptide, bombesin injected into the brain ventricule prevents gastric erosions-induced by 1-h cold restraint stress in rats

Treatment[a]	Dose (µg/rat)	Rectal temperature (°C)	Hemorrhagic gastric lesions Incidence (positive/total)	Hemorrhagic gastric lesions Severity (scale 0-3)
Saline	---	28.3 ± 0.4[b]	45/45[b]	2.0 ± 0.1[b]
Bombesin	5	26.4 ± 0.3**	2/15***	0.2 ± 0.1***
	1	27.2 ± 0.6*	2/10***	0.2 ± 0.1***
	0.5	26.0 ± 0.8NS	4/10***	0.5 ± 0.2***
	0.1	27.5 ± 0.8NS	5/10*	0.9 ± 0.4*
β-Endorphin	5	25.3 ± 0.4***	4/10***	0.4 ± 0.2***
	0.5	29.3 ± 0.6NS	5/5NS	1.4 ± 0.2NS
Neurotensin	5	27.5 ± 0.2NS	10/10NS	1.8 ± 0.2NS
Substance P	5	29.2 ± 0.4NS	10/10NS	2.3 ± 0.2NS
Somatostatin	5	30.2 ± 0.2*	11/11NS	1.8 ± 0.1NS
TRH	5	30.2 ± 0.4*	10/10NS	2.2 ± 0.2NS

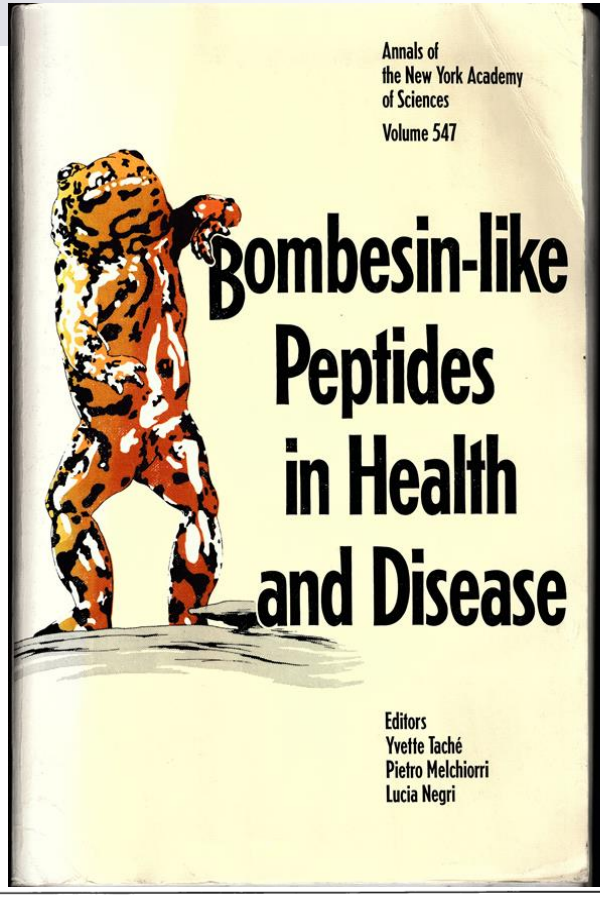
[a] The rats were fasted for 24 h and injected intraventricularly with saline or various doses of oligopeptides dissolved in saline. They were immediately immobilized in a cold room (4°C) for 1 h and decapitated. Rectal temperature was monitored before the injection (mean: 37.3 ± 0.1°C) and at the end of the 1-h cold+restraint period.

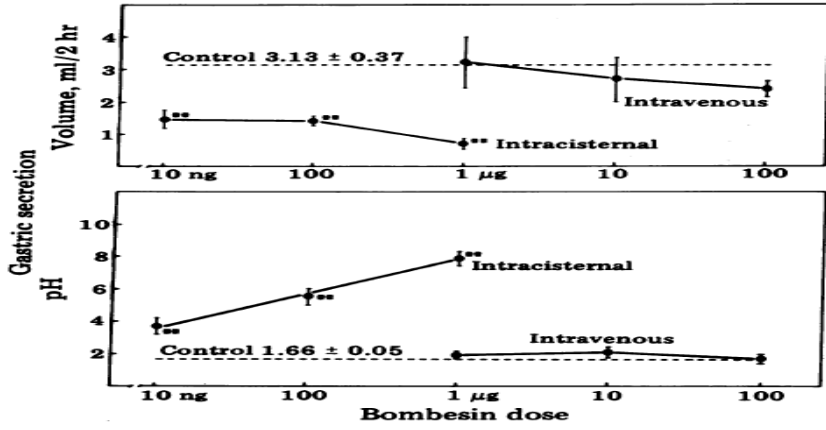
[b]

Martinez V and Taché Y. Bombesin and the brain-gut axis. Peptides 21:1617-1624, 2000

Bombesin is

- the first peptide shown to act in the brain to influence gastric function
- the most potent peptide to inhibit acid secretion when injected into the CSF
- acts in specific hypothalamic nuclei (PVN preoptic area and anterior hypothalamus), DVC, and T9-T10 spinal sites.
- induces an integrated gastric response (increase in bicarbonate, and mucus, inhibition of acid, pepsin, vagally mediated contractions) enhancing the resistance of the mucosa to injury through autonomic pathways.





Taché et al. Proc Natl Acad Sci 77:5515-9, 1980

From Selye Stress Concept to the Identification of the Biochemical Coding of Stress: Milestone Discoveries and Mentoring Linkage

Hans Selye, MD, PhD
McGill - Montreal Univ.

1936

Alarm Reaction/Stress

Selye's PhD Student, 1948-1953
Roger Guillemin, MD, PhD

Nobel price of Medicine, 1977

Salk Institute

TRH, LHRH, GHRH, Somatostatin, (1970-76)

Wylie Vale, PhD (1942-2012)
Guillemin's PhD Student-1962-65

1981	1993	1995	2001
CRF	Ucn 1 CRF_1	Ucn 2 CRF_2	Ucn 3

Jean Rivier, PhD

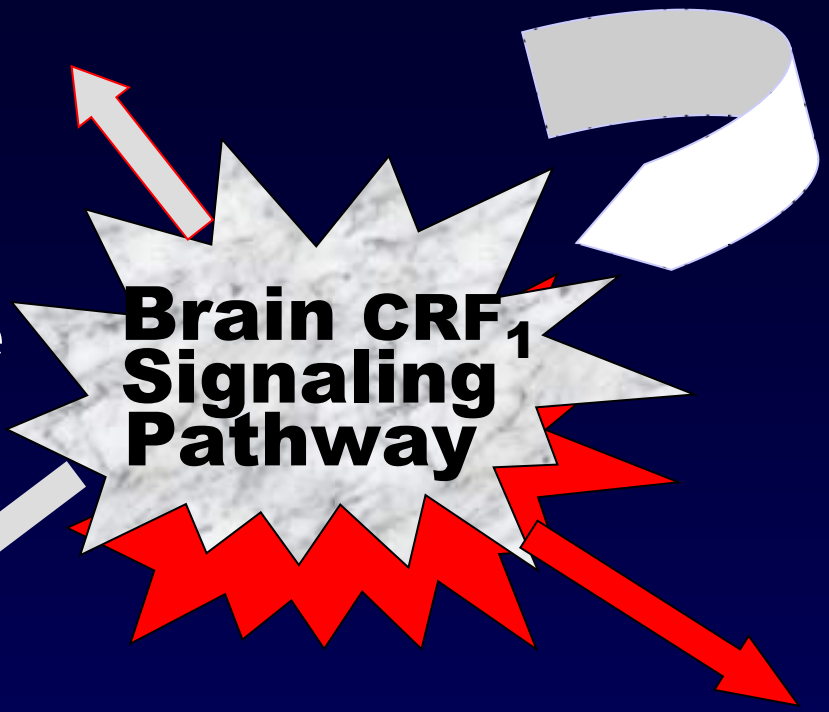
Peptide CRF receptor antagonist: α-helicalCRF_{9-41}, astressin, astressin-B, $astressin_2$-B

Stressors

Behavioral responses

- ↑ Anxiety
- ↓ Feeding
- ↑ Substance abuse

(craving, drug relapse)



Endocrine Response

↑HPA axis (↑ cortisol)

↓GH, LH, FSH

ANS responses

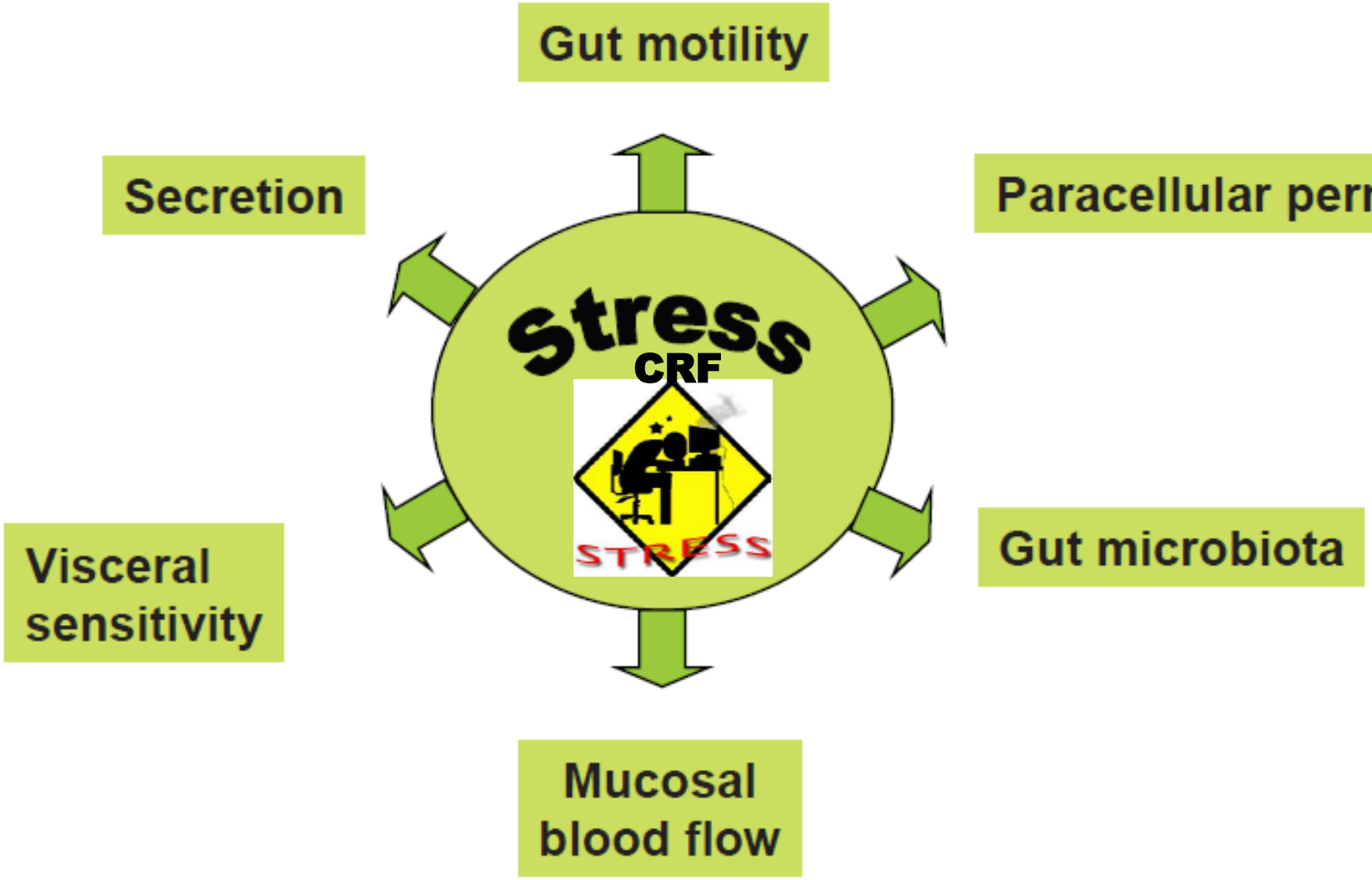
↑ Sympathetic outflow

↑ Noradrenaline release

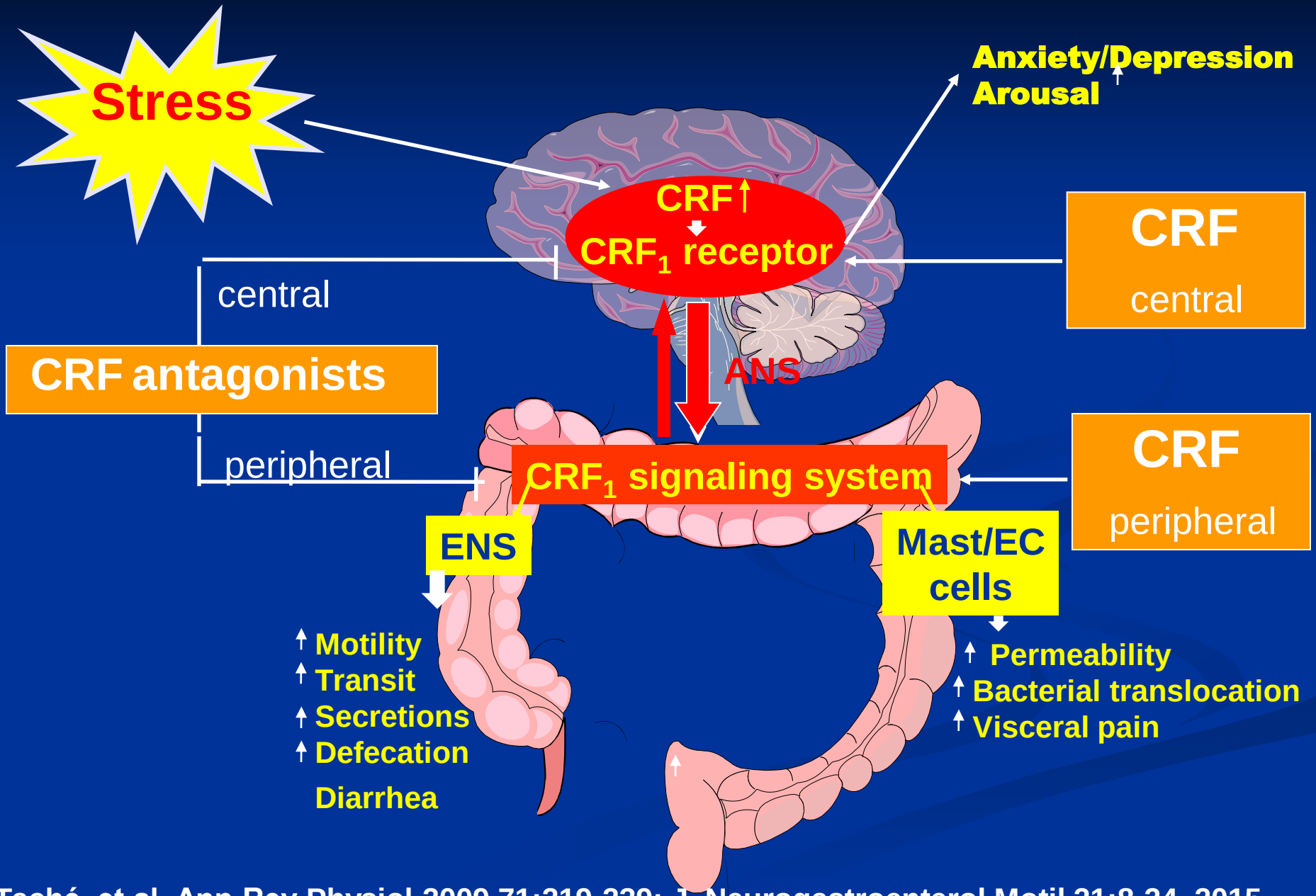
↓ Vagal outflow

↑ Sacral parasympathetic outflow

Stengel A, Taché Y. Exp Biol Med. 2010;235:1168-78; Zorrilla et al. Front Neuroendocrinol. 2014;35:234-44.


Gut motility
Secretion
Paracellular permeability
Stress
CRF
STRESS
Visceral sensitivity
Gut microbiota
Mucosal blood flow

CRF/CRF_1 receptors and the brain gut interactions

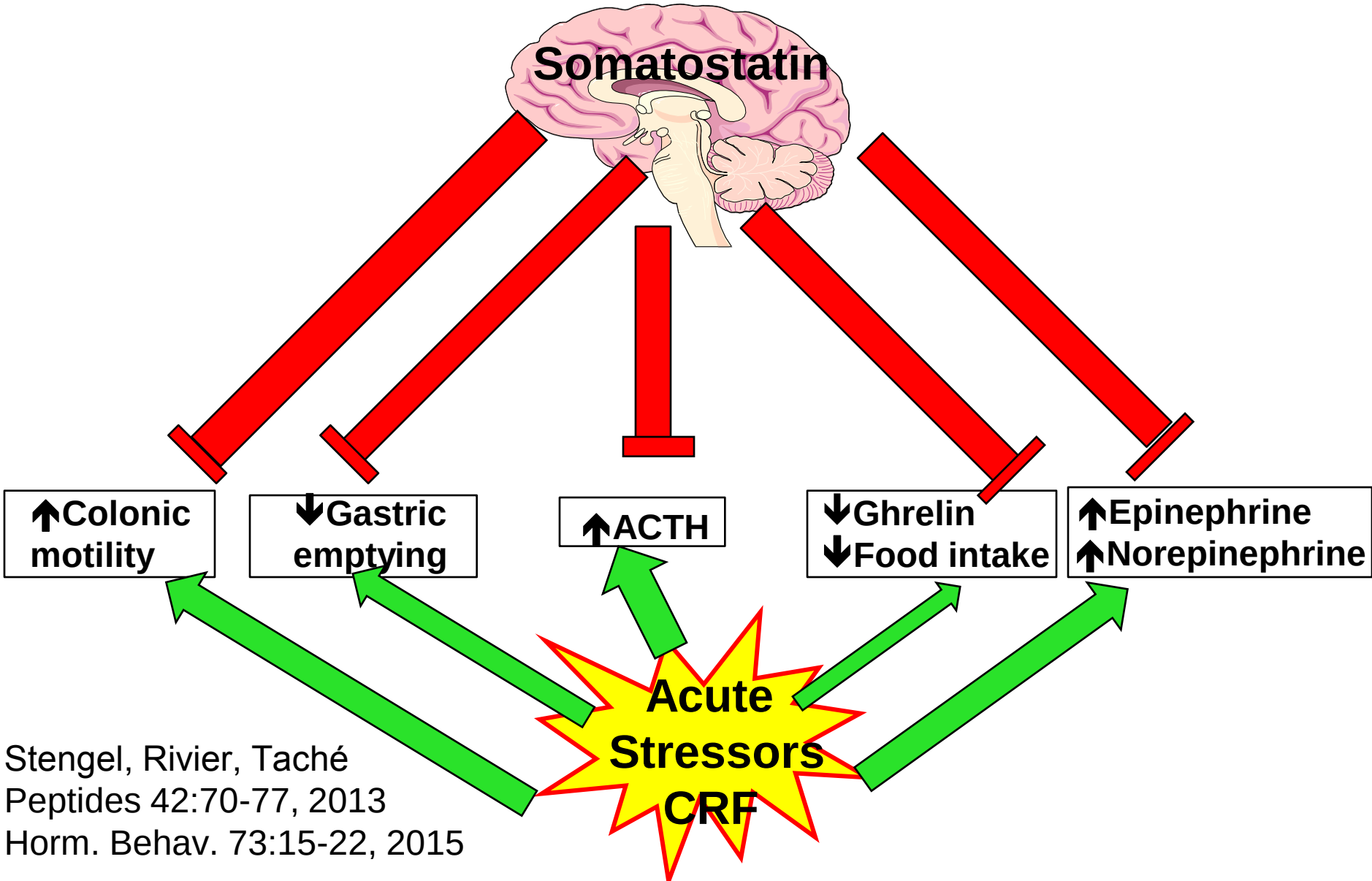


Taché et al. Ann Rev Physiol 2009 71:219-239; J. Neurogastroenterol Motil 21:8-24, 2015

Preclinical Studies Highlighting the Relevance of CRF_1 Receptor Blockade to Reduce IBS-like Symptoms

Characteristics in patients with IBS-D	In experimental animals, CRF_1 antagonists block stress-related:
Anxiety and/or depression	Anxiety/depression
Hypervigilance	Locus coeruleus activation/arousal
Changes in autonomic functions	Autonomic responses
Increased bowel movements /diarrhea	Stimulation of colonic motility/ defecation/diarrhea
Ion transport dysfunction	Colonic mucosal barrier dysfunction (increased secretion)
Mast cell changes (number, activation); low grade inflammation	Activation of colonic mast cells
Increase colonic permeability	Increase colonic permeability /antigen translocation
Lower pain threshold to colorectal distention	Hypersensitivity to colorectal distention

Activation of somatostatin signaling in the brain: a new anti-CRF-stress mechanism?



Stengel, Rivier, Taché
Peptides 42:70-77, 2013
Horm. Behav. 73:15-22, 2015

Former Fellows

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C. Maillot, MD
A. Stengel, MD
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M. Yoneda, MD

Research Associates

P-Q. Yuan, PhD
L. Wang MD, PhD
V. Wu Ph.D.

Collaborations with:

Salk Institute

J. Rivier, PhD; W. Vale, PhD

UCLA/VA investigators

J. Walsh, MD, P. Guth, MD, G. O/ning, MD, L. Chang, MD
E. Mayer, MD

Support NIHDDK (1982-present)

R01 DK 33061, DK 57238,
P30 DK 41301 (animal core), P50 DK 64539,

VA (2000-present)

Merit Award
Research Career Scientist

Celebration of Vale 65th birthday Salk Institute Symposium, 2007

W Vale Y Taché R. Guillemin