MTA/Hungarian Academy of Sciences, Budapest

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

From Steroids in the Selye Institute to CRF & IBS

Yvette Taché, PhD
Center for Neurobiology of Stress & CURE: Digestive Diseases Research Center, UCLA, and VA Los Angeles
Catatotoxic Steroids and the Modulation of Biological Function and Drug Actions


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


Endocrinology lab. Univ. Montreal, Montreal, Canada

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

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

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.
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.
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


CRF Ucn 1 CRF1 Ucn 2 CRF2 Ucn 3

Peptide CRF receptor antagonist:
α-helicalCRF9-41, astressin, astressin-B, astressin2-B

Jean Rivier, PhD

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

1970-76
TRH, LHRH, GHRH, Somatostatin, Salk Institute

1977
Nobel price of Medicine, 1977

Guillemin’s PhD Student - 1962-65
Behavioral responses

- ↑ Anxiety
- ↓ Feeding
- ↑ Substance abuse (craving, drug relapse)

Endocrine Response

- ↑ HPA axis (↑ cortisol)
- ↓ GH, LH, FSH

Brain CRF Signaling Pathway

ANS responses

- ↑ Sympathetic outflow
- ↑ Noradrenaline release
- ↓ Vagal outflow
- ↑ Sacral parasympathetic outflow

CRF/CRF₁ receptors and the brain gut interactions

Stress

CRF antagonists

central

peripheral

CRF₁ signaling system

ENS

Mast/EC cells

Motility
Transit
Secretions
Defecation
Diarrhea

↑ Motility
↑ Transit
↑ Secretions
↑ Defecation
↑ Diarrhea

CRF↑

CRF₁ receptor

ANS

CRFcentral

CRFperipheral

Anxiety/Depression
Arousal

Permeability
Bacterial translocation
Visceral pain

Preclinical Studies Highlighting the Relevance of CRF$_1$ Receptor Blockade to Reduce IBS-like Symptoms

<table>
<thead>
<tr>
<th>Characteristics in patients with IBS-D</th>
<th>In experimental animals, CRF$_1$ antagonists block stress-related:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety and/or depression</td>
<td>Anxiety/depression</td>
</tr>
<tr>
<td>Hypervigilance</td>
<td>Locus coeruleus activation/arousal</td>
</tr>
<tr>
<td>Changes in autonomic functions</td>
<td>Autonomic responses</td>
</tr>
<tr>
<td>Increased bowel movements /diarrhea</td>
<td>Stimulation of colonic motility/defecation/diarrhea</td>
</tr>
<tr>
<td>Ion transport dysfunction</td>
<td>Colonic mucosal barrier dysfunction (increased secretion)</td>
</tr>
<tr>
<td>Mast cell changes (number, activation); low grade inflammation</td>
<td>Activation of colonic mast cells</td>
</tr>
<tr>
<td>Increase colonic permeability</td>
<td>Increase colonic permeability/antigen translocation</td>
</tr>
<tr>
<td>Lower pain threshold to colorectal distention</td>
<td>Hypersensitivity to colorectal distention</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Name</th>
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</thead>
<tbody>
<tr>
<td>L. Barrachina</td>
<td>PhD</td>
</tr>
<tr>
<td>E. Barquist</td>
<td>MD</td>
</tr>
<tr>
<td>M. Larauche</td>
<td>PhD</td>
</tr>
<tr>
<td>A. Luckey</td>
<td>MD</td>
</tr>
<tr>
<td>V. Martinez</td>
<td>DVM, PhD</td>
</tr>
<tr>
<td>M. Million</td>
<td>DVM, PhD</td>
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<tr>
<td>C. Maillot</td>
<td>MD</td>
</tr>
<tr>
<td>A. Stengel</td>
<td>MD</td>
</tr>
<tr>
<td>H. Yang</td>
<td>PhD</td>
</tr>
<tr>
<td>M. Yoneda</td>
<td>MD</td>
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</tbody>
</table>

## Research Associates

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<tr>
<td>P-Q. Yuan</td>
<td>PhD</td>
</tr>
<tr>
<td>L. Wang</td>
<td>MD, PhD</td>
</tr>
<tr>
<td>V. Wu</td>
<td>Ph.D.</td>
</tr>
</tbody>
</table>

## 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 NHDDK (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