PAIN, CROSS ORGAN SENSITIZATION AND VISCERO-SOMATIC REFLEXES INVOLVING THE HEART

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PAIN, CROSS ORGAN SENSITIZATION AND VISCERO-SOMATIC REFLEXES

I. Introduction
  - Cross organ communication

II. Neurophysiology of Visceral Pain: The Heart
  - Spinal Cord Processing

III. Cross Organ Communication: Heart and Esophagus

IV. Cross Organ Communication: Heart and Gallbladder
  - Neurophysiology
  - Clinical Application

V. Cardio-Somatic Reflexes
  - Mechanisms
  - Effects of Diabetes

VII. Summary
CROSS-ORGAN COMMUNICATION
Viscero-visceral & Viscero-somatic Referred Pain
HYPOTHESIS
Jänig, Foreman & Other Investigators

Increased nociceptive input from one visceral organ or organ section sensitizes second-order neurons in the spinal dorsal horn (and possibly elsewhere) that receive convergent synaptic input from nociceptive afferent neurons of other visceral organs and of somatic tissues, in particular deep somatic ones.
Wilfrid Jänig
Commentary, Visceral pain – Still an enigma?
Pain 151 (2010) 239–240

“The phenomenon of viscero-visceral hyperalgesia clearly shows that the diagnosis of visceral pain requires careful investigation of all visceral organs that have common segmental projections of their visceral afferent neurons.”
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VII. Summary
THE ANGINA MAN
Ischemic Heart Disease

Netter, 1978
CIBA Collection
CHARACTERISTICS OF REFERRED PAIN (SPINO THALAMIC TRACT)

1. Pain of visceral origin referred to somatic regions that are innervated from the same spinal segments as the heart.
   a. cardiac afferents (T1-T5) chest and upper arm or arms
   b. vagal afferents neck and jaw
2. Pain is generally referred to proximal, but not distal somatic structures
3. Referred Pain is experienced as deep pain

Foreman
Ann. Rev. Physiol.61, 1999
POSTSYNAPTIC DORSAL COLUMN (PSDC) PATHWAY: Transmits pelvic & pancreatic pain

POSTSYNAPTIC DORSAL COLUMN PATHWAY: DOES IT TRANSMIT CARDIAC NOCICEPTIVE INFORMATION?

RESPONSES OF POSTSYNAPTIC DORSAL COLUMN (PSDC) AND T3 SPINOthalamic TRACT (STT) NEURONS TO CARDIAC STIMULI IN RATS

Mechanical Stimulation

<table>
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<tr>
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<th>STT</th>
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<tbody>
<tr>
<td>Mechanical</td>
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<tr>
<td>Stimulation</td>
<td>43%</td>
<td>66%</td>
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Intrapericardial Bradykinin

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Bradykinin</td>
<td>14%</td>
<td>100%</td>
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</tbody>
</table>

* p=0.0003, Fisher’s Exact Test

POSTSYNAPTIC DORSAL COLUMN PATHWAY: DOES IT TRANSMIT CARDIAC NOCICEPTIVE INFORMATION? NO!

Upper thoracic postsynaptic dorsal column neurons conduct cardiac mechanoreceptive information, but not cardiac chemical nociception in rats.

ARE CAPSAICIN-SENSITIVE (TRPV-1 Receptors) SENSORY NERVES INVOLVED IN CARDIAC NOCICEPTION?

CHARACTERISTICS OF TRPV1

TRPV1:

• Non selective-cation channel
• Activated by capsaicin, heat and hydrogen ions.
• Found mainly in nociceptive neurons
• Influx of cations after activation
• Related to the pathogenesis of inflammation and cardiovascular diseases.
• Sensitized by prostaglandins and bradykinin

TRPV1: Transient receptor potential vanilloid-1
**DESENSITIZATION OF TRPV-1 RECEPTORS IN SENSORY FIBERS: EFFECTS ON SPINAL PROCESSING**

- Resiniferatoxin (RTX)
- An ultra-potent capsaicin agonist
- A useful chemical agent to specifically target and desensitize TRPV-1 containing sensory fibers.

**Administration of RTX in the pericardial sac**

- Sensitization (15-20 min)
- Desensitization (Hours)
- Destroy fibers (Days)

Nerve terminals containing TRPV1 receptors in the heart.

**Intrapericardial RTX (0.2 µg/ml, 0.2 ml, 1 min)**
EFFECT OF INTRAPERICARDIAL RTX ON ACTIVITY OF T3 SPINAL NEURON TO BRADYKININ OR CAPSAICIN (CAP)

SUMMARY OF EXCITATORY RESPONSES TO INTRAPERICARDIAL CHEMICALS BEFORE AND AFTER SENSORY NERVE DESENSITIZATION USING RTX

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VII. Summary
GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Second most frequent cause of chest pain
- Can produce typical anginal pain in patients with coronary artery disease
- Can significantly reduce coronary blood flow velocity and volume
- Can generate cardiac arrhythmias
- Can elicit ischemic ECG changes
CROSS-ORGAN SENSITIZATION BETWEEN VISCERAL ORGANS

- Spinothalamic Tract (Nociception, Pain)
- T3-T4 Segments Spinal Visceral Afferents
- Dorsal Root Ganglion (DRG)
- Esophagus
GASTROESOPHAGEAL REFLUX (GER) INDUCTION

- Anesthetize rat and expose stomach
- Ligate the pylorus of the stomach
- Ligate junction between forestomach and corpus
- Longitudinal myelotomy across the gastro-esophageal junction
- Cell recordings were made 4-8 hours after ligation and myelotomy
HISTOLOGICAL EXAMINATION: ESOPHAGITIS IN RATS WITH GER AND CONTROL SURGERY

CONTROL

GER

Qin C, Malykhina AP, Thompson AM, Farber JP, Foreman RD
Am. J. Physiol. 298: G934-G942, 2010
A, Cell recording at T3-T4 segments; B, Intrapericardial Sac Injections of Chemicals
RESPONSE PATTERNS OF T3 SPINAL NEURONS TO IB IN CONTROL AND GER ANIMALS

GER = Gastroesophageal Reflux
IB = Intrapericardial Bradykinin

Qin C, Malykhina AP, Thompson AM, Farber JP, Foreman RD
Am. J. Physiol. 298: G934-G942, 2010
RESPONSE CHARACTERISTICS OF T3-T4 SPINAL NEURONS RECEIVING NOXIOUS CARDIAC INPUT (IB) IN GER AND CONTROL ANIMALS

![Graph showing response characteristics of T3-T4 spinal neurons receiving noxious cardiac input (IB) in GER and control animals. The graph compares the Imps/s response to SA and IB in control and GER conditions. The response to IB in GER is significantly higher (P<0.01) compared to control.](image)

GER = Gastroesophageal Reflux
IB = Intrapericardial Bradykinin

Qin C, Malykhina AP, Thompson AM, Farber JP, Foreman RD
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GALLBLADDER DISEASE

- Gallbladder attacks can cause severe pain of the upper abdomen, back, and chest.
- Gallbladder attacks can mimic pain of angina pectoris and heart attack.
- In men, a history of angina pectoris is a significant predictive factor for development of biliary stones.
VISCERO-VISCERAL INTERACTIONS BETWEEN THE HEART AND GALLBLADDER

SCHEMATIC DIAGRAM: ELECTRICAL STIMULATION OF THE CARDIOPULMONARY AFFERENTS AND THE SPLANCHNIC NERVES

ELECTRICAL STIMULATION
A—Cardiopulmonary Nerves
B—Greater Splanchnic Nerve
C—Lesser Splanchnic Nerve

RESPONSES OF A UPPER THORACIC (T4) SPINOthalamic TRACT CELL TO ELECTRICAL STIMULATION OF THE SPLANCHNIC (SPL) OR CARDIOPULMONARY (CP) AFFERENT FIBERS

RESPONSE OF A T4 SPINOthalamic tract cell to noxious gall bladder distension

Rate (Imp/S)

Unit

ECG

BP (mm Hg)

HR (BPM)

GBP (mm Hg)

RESPONSES OF GALL BLADDER-RESPONSIVE AND NONRESPONSIVE T3-T5 SPINOPTHALAMIC CELLS TO BRADYKININ INJECTIONS IN THE HEART

PATHWAY FOR SPLANCHNIC INPUT

Effects of transecting the Sympathetic Chain or the Spinal Cord on Splanchnic Activation of Spinothalamic Tract Cells

**A**

<table>
<thead>
<tr>
<th>Region</th>
<th>% Control</th>
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<tbody>
<tr>
<td>T5-T6</td>
<td>100</td>
<td>3</td>
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<tr>
<td>T6-T7</td>
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<td>T7-T8</td>
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<td>3</td>
</tr>
<tr>
<td>T8-T9</td>
<td>50</td>
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**B**

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<tr>
<th>Region</th>
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<tr>
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<td>100</td>
<td>4</td>
</tr>
<tr>
<td>LAT</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>VLAT</td>
<td>50</td>
<td>2</td>
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</tbody>
</table>

Ammons WS, Blair RW, Foreman RD
J. Neurophys. 51: 592-603, 1984
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VII. Summary
TRANSLATIONAL RESEARCH
Bench to Bedside and Back Again
Peter J. Schwartz, MD
Milan, Italy
Cardiologist
1974-2011

J. Andrew Armour, MD, PhD
1969-2011

Bengt Linderoth, MD, PhD
Stockholm, Sweden
Neurosurgeon
1996-2011

Philip B. Adamson, MS, MD
Oklahoma City, OK
Cardiologist
1999-2011

Michael J. DeJongste, MD, PhD
Groningen,
The Netherlands
Cardiologist
1996-2011

MY LIFE IN TRANSLATION
Co-existing algogenic conditions in two internal organs in the same patient may mutually enhance pain symptoms (viscero-visceral hyperalgesia).

Results of patients with coronary artery disease or gall bladder stone or both (common projections of the visceral afferent neurons to spinal segment T5)

VISCERO-VISCERAL HYPERALGESIA: CHARACTIZATION OF DIFFERENT CLINICAL MODELS

Viscero-visceral hyperalgesia in patients with Coronary Artery Disease (CAD) and Gallstone (Gs)

Sites of pain threshold measurement within the referred pain areas. Left anterior chest area for cardiac pain (pressure pain thresholds-PPTs)

HEART-GALL BLADDER INTERACTIONS
Cardiac symptoms

Number of angina episodes

Muscle Pain Thresholds (Chest)

CAD—Coronary Artery Disease
Gs—Gallbladder Stone-Cholecystitis
Kg-f/s—kilogram-ft/sec

HEART-GALL BLADDER INTERACTIONS

Cardiac symptoms before and after Cholesystectomy (CholecystX)

Number of angina episodes

Muscle Pain Thresholds (Chest)

IMPLICATIONS OF VISCERO-VISCERAL HYPERALGESIA

- Diagnosis of visceral pain will require a careful investigation of all visceral organs having overlapping segmental projections of afferent fibers.

- Treating pain of a particular organ will likely reduce pain for other visceral organs with overlapping segmental innervation.

- Experiments need to be designed to unravel peripheral and central mechanisms of visceral pain.

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VII. Summary
VISCERAL NOCICEPTIVE STIMULUS

Visceral Nociceptive Stimulus

Visceral Pain

Minutes → hours

Referred

Viscera

Muscle

Skin

Modified from Arendt-Nielsen, 2000
SEGMENTAL DISTRIBUTION OF INCREASED PARASPINAL TONE CHRONIC CARDIAC DISEASES

Adapted from Larson, 1976; in
In “The Science and Clinical Application of Manual Therapy”
HYPOTHESIS

Cardio-somatic reflexes generate motor contractions.

Motor contractions sensitize muscle afferents to generate muscle pain, which is ultimately experienced as a part of CARDIAC PAIN.


Jerry Jou, DO, PhD
Algogenic Chemicals
• bradykinin
• serotonin
• prostaglandin E2
• histamine
PARASPINAL MUSCLES SCREENED USING CARDIO-SOMATIC MOTOR REFLEXES

Measurement of Response
Bipolar wire electromyography (EMG) recordings (25-gauge needle, 30° angle, 1.5-1.7 mm deep)

AC Acromiotrapezius
LD Latissimus dorsi
RC rhomboideus capitis
RT Rhomboideus trapezius
SPL Splenius
SPT Spinotrapezius
CARDIO-SOMATIC MOTOR REFLEXES

Typical Raw EMG
CARDIAC-EVOKED EMG ACTIVITIES OF SPINOTRAPEZIUS MUSCLE

n=53

Discharge rate (imp/sec) vs Time (sec)

Algesic Chemical Injection Pericardial Sac
LEFT SYMPATHETIC CHAIN TRANSECTION
MOTOR RESPONSE TO ALGOGENIC INFUSION

TMUP (imp)

* Repeated ANOVA, followed by Tukey

* , P<0.01

Intact
60 minutes after transection
120 minutes after transection

TMUP = Total # of Motor Unit Potentials
ELECTRICAL STIMULATION

Left Sympathetic Chain

Vagal Afferents
BILATERAL VAGOTOMY
MOTOR RESPONSE TO ALGOGENIC INFUSION

* Repeated ANOVA

*, P<0.05

Vagi Intact

60 minutes after transection

TMUP = Total # of Motor Unit Potentials
NRM/PAG/PB-SC = Nucleus Raphe Magnus/Periaqueductal Gray/Parabrachial-Subcoeruleus
NTS = Nucleus Tractus Solitarius
SAN = Spinal Accessory Nucleus

PATHWAYS OF CARDIO-SOMATIC MOTOR REFLEXES

- inhibition
- excitation
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LINK BETWEEN DIABETES AND CARDIOVASCULAR DISEASE

• About 65% of people with diabetes die from heart disease and stroke
• Adults with diabetes are 2 to 4 times more likely to have heart disease or suffer a stroke than people without diabetes
• People with type 2 diabetes also have high rates of high blood pressure, lipid problems, and obesity.
• Smoking doubles the risk for cardiovascular disease in people with diabetes
Diabetic rats show reduced cardiac-somatic reflex evoked by intrapericardial capsaicin

X-H Liu, C Qin*, J-Q Du, Y Xu, N Sun, J-S Tang, Q Li, RD Foreman

European Journal of Pharmacology 651 (2011) 83-88

* In Memory of Dr. Chao Qin
EXPERIMENTAL SETUP

Capsaicin

EMG

Amp
CHANGES IN BLOOD GLUCOSE CONCENTRATION (A), BODY WEIGHT (B) AND MECHANICAL PAW TRESHOLD IN DIABETIC AND CONTROL RATS
EMG ACTIVITY
Electrical Stimulation Left Sympathetic Chain

Control

Diabetic

Electrical Stimulation

100μV

5s
EMG ACTIVITY
Electrical Stimulation Left Sympathetic Chain

![Chart showing EMG activity with data points for EMG rate and EMG duration.](chart)

- EMG Rate: Diabetic 42 vs Control 43
- EMG Duration: Diabetic 33 vs Control 35

Impulses/s vs seconds (Diabetic vs Control)
EFFECTS OF CAPSAICIN ALONE OR COMBINED WITH TRPV1 ANTAGONIST, CAPSAZEPINE, ON EMG ACTIVITY

![Graph showing effects of capsaicin and capsaizepine on EMG activity.](image-url)
DIABETIC RATS
Summary & Conclusions

• Capsaicin-induced cardio-somatic reflex activity was decreased in diabetic rats
• Capsaicin induced cardio-somatic reflex was decreased by capsazepine
• Abnormal cardiac nociception may involve reduced TRPV1 function or fewer cardiac afferents expressing TRPV1
• Changes in transmission of cardiac information might contribute to silent ischemia observed more commonly in diabetic patients
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NEURAL MECHANISMS UNDERLYING ANGINA PECTORIS

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Foreman
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Dorsal Root Ganglion (DRG)

Esophagus
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PATHWAYS OF NRM/PAG/PB-SC

CARDIO-SOMATIC MOTOR REFLEXES

NRM/PAG/PB-SC = Nucleus Raphe Magnus/Periaqueductal Gray/Parabrachial-Subcoeruleus
NTS = Nucleus Tractus Solitarius
SAN = Spinal Accessory Nucleus

inhibition
excitation
AKNOWLEDGMENTS

• Spinothalamic Tract Cells, Spinal Processing Stimulation
  – Dr. Chao Qin
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  – Dr. Melanie Goodman-Keiser
  – Dr. Kenneth Miller
  – Dr. Ann Thompson
  – Dr. Anna Malykhina
  – Dr. Nadia Girardot

• Cardiosomatic Reflexes
  – Dr. C. Jerry Jou
  – Dr. Chao Qin
  – Xi’an Jiaotong University, Xi’an, China

• NIH National Heart Lung and Blood Institute
• NIH National Institute of Nervous System & Stroke
• National Natural Science Foundation of China

TEAMWORK
THE OKLAHOMA CITY NATIONAL MEMORIAL
"WE COME HERE TO REMEMBER"

THANK YOU