Neural Regulation of the Heart
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Control of Heart Rate
(a) The conducting system and sinoatrial node
Sinotrial (S-A) node
Left atrium
Right atrium
Atrioventricular (A-V) node
Fibrous connective tissue
Left bundle branch
Right bundle branch
Right ventricle
Left ventricle
Interventricular septum

(b) Membrane potential (mV)
Ca²⁺ channels close; K⁺ channels open
Ca²⁺ permeability
K⁺ permeability
Action potential
Slow depolarization: Pacemaker potential
Threshold

Time (ms)
Sensory innervation

**Sensory Inputs**
- BP
- pH
- pO\textsubscript{2}

CNS Preganglionic Neurons

Parasympathetic Cardiac Ganglion

- Fast synaptic transmission (ionotropic)
  - ACh (nicotinic receptors)
- Other signals (metabotropic)
  - ACh (muscarinic receptors)
  - NE
  - Neuropeptides
  - Locally-generated signals
    - Inflammatory signals

Neuropeptides

- **Neuropeptides**
  - Sensory peptides (sensory neurons from spinal cord)
    - Substance P
    - CGRP
  - Parasympathetic fibers
    - PACAP (parasympathetic neurons from brainstem, neurons within ganglion)
      - PACAP38, PACAP27
  - Sympathetic fibers
    - Neuropeptide Y (sympathetic postganglionic fibers)
Cardiac Mast Cells

- Found in high density in mammalian heart
- Stimulated by:
  - Antigen exposure
  - Sensory neuropeptides
  - Chemoreceptors
  - pH changes, low oxygen
- Upon stimulation, release
  - Histamine
  - Prostaglandins

Parasympathetic Cardiac Ganglion

Sensory Afferents

Model System

- Guinea pig cardiac ganglion

Substance P
Guinea pig cardiac ganglion

“puffer” containing test substance
Neuromodulation

- **Acute changes**
  - Changes in excitability
  - Changes in sensitivity to individual chemicals
  - Changes in synaptic function
- **Long term changes**
  - Changes in phenotype

**Histamine**

![Histamine Depolarization Mechanism](image)

![Control](image)  ![Histamine](image)
### Sodium Channels: Ion substitution

#### Membrane Depolarization

<table>
<thead>
<tr>
<th></th>
<th>Amplitude</th>
<th>Duration</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.6 ± 2.8</td>
<td>46.9 ± 29.4</td>
<td>19</td>
</tr>
<tr>
<td>50% NMG</td>
<td>4.0 ± 1.5</td>
<td>54.3 ± 18.4</td>
<td>6</td>
</tr>
<tr>
<td>100% NMG</td>
<td>2.0 ± 1.1</td>
<td>33.9 ± 35.1</td>
<td>9</td>
</tr>
</tbody>
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NMG = N-methylglucamine (positive ion, cannot move through Na⁺ channels)

### Excitability Changes: Ion Channel Inhibitors

- How can you change the firing properties of a neuron?
- What ionic mechanisms could produce this?

- Barium
  - Blocks many K channels, including some leakage channels and m-current
- 4-aminopyridine
  - Blocks A-current (K channel)
- TEA
  - Blocks some Ca-dependent K channels
- Cs⁺
  - Blocks H-current (hyperpolarization-activated cation channel)
Control

1 mM Cs⁺

1 mM 4-AP

1 mM Ba²⁺

5 mM TEA

Remove external Ca²⁺

200 µM Cd²⁺

Muscarinic Receptors

• Preganglionic fibers (from brainstem)
  • ACh - nicotinic (fast) and muscarinic (slow)
  • Bethanechol – muscarinic agonist
Adrenergic Receptors

- Adrenergic postganglionic fibers
- NE – increase excitability

Single Action Potentials

PACAP
Excitability Changes

- Histamine
  - Dependent on influx of extracellular Calcium ions
  - TRPC channel?
- Muscarinic (bethanechol)
  - TEA-sensitive channels
  - BK channels? M-current?
- Adrenergic
  - Calcium-dependent
  - Indirect inhibition of BK channels?
  - VDCC?
- Neuropeptides
  - PACAP
  - H channels, Calcium-dependent mechanism
  - Internalization of receptors

Long term changes: Remodeling

- Chronic heart disease
- Number one cause of death in the United States
  - 2010 data: 595,444 deaths due to heart disease
  - ~24% of all deaths
  - Ischemic heart disease (heart attacks) most common form

*How does neuronal control of the heart change with chronic heart disease?*
Models of Heart Disease

- Myocardial infarction (MI)
  - Ligate left ventricular coronary artery
  - 6-9 weeks recovery
- Pressure Overload (PO)
  - Band descending dorsal aorta
  - Produces left ventricular hypertrophy
  - 8-10 weeks recovery
- Sham surgery


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