Neural Regulation of the Heart

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Control of Heart Rate

(a) The conducting system and sinoatrial node

- Sinuatrial (S-A) node
- Right atrium
- Atrioventricular (A-V) node
- Atrioventricular bundle
- Left bundle branch
- Right bundle branch
- Right atrium
- Left atrium
- Interventricular septum
- Left ventricle
Preganglionic neuron

Postganglionic neuron

Cardiac Ganglion

Parasympathetic:

Sympathetic:
Sensory innervation

**Sensory Inputs**
- BP
- pH
- pO₂

**CNS Preganglionic Neurons**

**Parasympathetic**
- Cardiac Sensory Neurons
- Parasympathetic Postganglionic Neurons
- Cardiac Target Cells

**Sympathetic**
- Cardiac Sensory Neurons
- Parasympathetic Postganglionic Neurons
- Cardiac Target Cells

**Parasympathetic Cardiac Ganglion**
- Fast synaptic transmission (ionotropic)
  - ACh (nicotinic receptors)
- Other signals (metabotropic)
  - ACh (muscarinic receptors)
  - NE
  - Neuropeptides
  - Locally-generated signals
    - Nitric Oxide (NO)
    - Inflammatory signals

**Neuropeptides**
- Neuropeptides
  - Sensory peptides (sensory neurons from spinal cord)
  - Substance P
  - CGRP
  - PACAP (neurons from brainstem, neurons within ganglion)
Nitric Oxide

- Three isoforms of nitric oxide synthase
  - Neuronal NOS (nNOS)
  - Endothelial NOS (eNOS)
  - Inducible NOS (iNOS)

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

- Preganglionic Fibers
- Postganglionic Fibers
- Sensory Afferents
Model System

- Guinea pig cardiac ganglion

Nitric Oxide in the Heart

nNOS

MAP2

Guinea pig cardiac ganglion

"puffer" containing test substance

Preganglionic fiber

Postganglionic neuron

Phasic Neuron

Tonic Neuron

Neuromodulation

- Acute changes
- Changes in excitability
- Changes in sensitivity to individual chemicals
- Changes in synaptic function

- Long term changes
- Changes in phenotype
Histamine

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>
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</tbody>
</table>

Depolarization Mechanism?
How can you change the firing properties of a neuron?

What ionic mechanisms could produce this?

Excitability Changes: Ion Channel Inhibitors

- 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)
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

A

Krebs  0 Calcium  5 mM TEA

Control

NE

Bath

A

control

PACAP

C

Ca²⁺-deficient

Ca²⁺-deficient + PACAP

A

control 13°C

PACAP 13°C

2

Control 22°C

PACAP 22°C

3

Control 22°C

B 32°C

C

Control 32°C

PACAP 32°C

30 mV

500 ms

0 -

Cs⁺

Cs⁺ + PACAP

0 -
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

Synaptic Function

- Preganglionic fiber
- Postganglionic neuron

Synaptic Transmission

- Nitric Oxide

<table>
<thead>
<tr>
<th>Control</th>
<th>SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPSP Amp (mV)</strong></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.1 ± 1.6 ( (N=6) )</td>
</tr>
<tr>
<td>SNP</td>
<td>7.4 ± 3.5 ( (N=6) )</td>
</tr>
</tbody>
</table>

\* \( p < 0.02 \), paired T test

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


Regulation of NOS levels

- Control
- Chronic MI

nNOS and MAP2

Regulation of NOS levels

- % nNOS Neurons
- qPCR – nNOS mRNA

Synaptic Function

Preganglionic fiber
Postganglionic neuron
Synaptic Function

- EPSPs

<table>
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<tr>
<th></th>
<th>CONTROL</th>
<th>MI</th>
<th>PO</th>
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</thead>
<tbody>
<tr>
<td>RMP (mV)</td>
<td>-49.5 ± 7.9</td>
<td>-41.8 ± 5.8</td>
<td>-46.7 ± 9.1</td>
</tr>
<tr>
<td>EPSP amplitude (mV)</td>
<td>6.8 ± 0.4</td>
<td>6.6 ± 0.6</td>
<td>5.6 ± 0.8</td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>19</td>
<td>17</td>
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No significant differences

What could produce this change in synaptic function?
### Synaptic Changes

- No changes in EPSP amplitudes with chronic disease
- No apparent changes in synaptic function in animals with MI
- Enhanced synaptic function ONLY in animals with PO
- Increased function is not inhibited by atropine (not due to increased sensitivity to muscarinic activity)

### Drug Treatment

- Implant osmotic pump
- NE blocker
- Timolol
  - Blocks $\beta$-adrenergic receptors
- Induce heart disease
- 2 weeks later, implant pump
- Total drug treatment period of 6 weeks
- Control animals, just drug, no disease
Adrenergic Blocker: Timolol

MI Time Course
- Induce MI
- Examine tissue at
  - 4 Days
  - 7 Days
  - 14 Days
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- Lauren Houdek ’09
- Stephanie Hinsvark ’12

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The Heart Nebula