Neural Regulation of the Heart

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Control of Heart Rate

Controlled by autonomic nervous system

Sympathetic effect

Parasympathetic effect

Threshold Potential

Pacemaker Potential

Threshold Potential

Pacemaker Potential

NEUROSCIENCE, Fourth Edition, Figure 24.1
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)
  - PACAP38, PACAP27

Sensory innervation

- Sensory Inputs
  - BP
  - pH
  - pO₂

Parasympathetic:

Cardiac Sensory Neurons

- CNS Preganglionic Neurons
- Parasympathetic Postganglionic Fibers
- Cardiac Sensory Neurons
- Cardiac Target Cells

Sympathetic:

- Thoracic Ganglia
- Parasympathetic Postganglionic Neurons
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

Model System
- Guinea pig cardiac ganglion

Nitric Oxide in the Heart

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

Depolarization Mechanism?
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>
</table>

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
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></th>
<th>EPSP Amp (mV)</th>
</tr>
</thead>
<tbody>
<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>
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</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

- % nNOS cells

**Control**

**Sham surgery**

**MI**

**PO**

Regulation of NOS levels

**IHC - % nNOS Neurons**

**qPCR – nNOS mRNA**

Synaptic Function

- EPSPs

<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>MI</th>
<th>PO</th>
</tr>
</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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</tbody>
</table>

No significant differences

Synaptic Function

- Suprathreshold stimulations
  - 20 Hz, 2 sec duration
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**
- 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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- Melanie Powers Frazier ’01, Ally Girasole ’10
The Heart Nebula