Cardiotoxicity of Hyperamylininemia

Amylin Oligomers

Calcium dysregulation

Hypertrophy, Remodeling

Heart Failure

Hyperamylininemia

Hyperglycemia

Hyperinsulinemia

Pancreatic β-Cell

β-Cell Dysfunction & Apoptosis

Amylin Oligomerization

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Patients with Obesity and Type-2 Diabetes Present Cardiac Amylin Accumulation

A source of cardiomyocyte Ca$^{2+}$ dysregulation

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Funds: AHA, NSF, Vision Grant - UC Davis
HYPOTHESIS

Type-2 Diabetes

Risk for Cardiac Disease

Insulin Resistance

Insulin
type

Hyperamylinemia

Hyperinsulinemia

BLOOD

pancreatic β-cell

Insulin

amylin

Toxic Amylin Oligomers

HF

Dyslipidemia

Hyperglycemia
**RATIONALE:** selection of human heart samples

Lean Non-Failing Hearts

Lean, Non-diabetes Failing Hearts

Obese/Overweight Non-Failing Hearts

Obese/Overweight Failing Hearts

Type-2 Diabetes Failing Hearts

Amylin Oligomers

distinct amylin oligomer size distributions
Amylin Oligomers Accumulate in Heart

Failing vs. Non-failing

Anti-Amylin Antibody

Amylin Trimers (% Control)

Amylin Level (% Control)

Larger Amylin Oligomers

16-MER
OCTAMER
TETRAMER
TRIMER
DIMER

FAILING
NON-FAILING

L-NF  OW/OB-HF

octamer

tetramer

trimer

Amylin Oligomers

**

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Cardiac Amylin Deposition in Type-2 Diabetic Humans
Amylin Oligomers Circulate Through the Blood Obese, Diabetes and Kidney Failure

**Obesity and Type-2 Diabetes**

**With Kidney Failure**

[Graph showing IAPP levels in different conditions]
Acute Effect of Amylin on Isolated Cardiac Myocytes

Human: KCNTATCATQRLANFLVHSSNNFGAILSSSTNVGSNTY
Rat:  KCNTATCATQRLANFLVRSSNNLGPVLPPTNVGSNTY

![Graph showing the effect of amylin on intracellular calcium concentration and transient decay. The graph compares control, h-amylin, and r-amylin treatments across different frequencies.](image-url)
Amylin Oligomers Alter the Structure of Sarcolemma in Isolated Cardiac Myocytes

\[ \text{Thaps} + \text{0Ca/0Na} + \text{carboxyeosin} \]

[Graph showing [Ca\(^{2+}\)]\(_i\) (nM) vs time (1 min) with Amylin and Ctl curves]

[Bar graph showing Passive Ca\(^{2+}\) Leak withCtl and Amylin (control)]

[Images showing 2.5 µm scale with arrows indicating changes in sarcolemma structure]
Animal Models

Human Amylin pancreas

Rat Amylin pancreas

HIP rat

UCD-T2DM rat

Non-fasting Blood Glucose Level

<table>
<thead>
<tr>
<th>Blood Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>HIP</td>
</tr>
<tr>
<td>UCD-T2DM</td>
</tr>
</tbody>
</table>
Amylin Accumulates in the Heart of HIP Rats

HIP rat

HIP rat

UCD-T2DM rat

Pancreas
Heart
Pancreas
Heart

20 µm

20 µm

25 kDa
15 kDa
10 kDa

25 kDa
15 kDa
10 kDa

Lysates
PD
DM

16 kDa
Myocardial Insulin Signaling in HIP vs. UCD-T2DM rats

![Graph showing p-Akt/Akt (a.u.) levels in Ctl, HIP, and UCD groups with insulin levels of 0, 10, and 10. The graph indicates a significant increase in p-Akt/Akt levels in HIP and UCD groups compared to Ctl group.]
Cardiac Amylin Oligomer Accumulation Alters Ca^{2+} Cycling in HIP Rats

**HIP rat**

**UCD rat**

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**Diastolic dysfunction**

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**Decay time (s)**

---

**Frequency (Hz)**

---

**[Ca]_i (nM)**

---

**Systolic**

---

**Diastolic**

---

**Ctl**

---

**HIP**

---

**UCD**

---

**Ctl**

---

**HIP**

---

**UCD**

---

**Ctl**

---

**HIP**

---

**UCD**

---

**Ctl**

---

**HIP**

---

**UCD**

---

**Ctl**

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**HIP**

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**UCD**

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Contractile Dysfunction in Pre-diabetic HIP Rats

collab. with A. Knowlton (UC Davis)
Cardiac Amylin Oligomer Accumulation Triggers Remodeling of SERCA

**HIP rat**

**UCD rat**

![Graph and images showing changes in SERCA, PLB, and NCX proteins in Ctrl, PD, and DM conditions.](Image)