Cardiovascular Consequences of Metabolic Disease

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Cardiovascular Consequences of Metabolic Disease

Current resources:
3 program grants:

• AMPK, Endothelial Cell Dysfunction, and the Metabolic Syndrome
  (PI Ruderman, Walsh, Cohen)

• Metabolic Control of Endothelial Cell Phenotype
  (PI Walsh, Vita, Cohen, Gokce, Loscalzo)

• Vascular Consequences of Insulin Resistance and Obesity
  (PI Vita, Gokce, Freedman, Hamilton)
Factors secreted from fat involved in crosstalk between adipocytes, macrophages and vascular cells

ARC Goals:

Foster cooperation between basic science and clinical labs investigating:

1) Fat as an endocrine organ

2) The vascular-protective effects of polyphenols (resveratrol); potential roles of Sirtuin-1, AMP kinase, and Adiponectin

3) The role of obesity-associated inflammation in microvascular dysfunction
Adipose tissue functions as an endocrine organ

**Adiposity**

- TG

**“Adipokines”**

- TNFα
- Leptin
- Resistin
- IL-6

**Cardiovascular disease**

- Protective
- Harmful

- Adiponectin

**Hypo-adiponectinemia**

- Coronary heart disease
- Type 2 diabetes
- Hypertension
- Stroke
- etc.

**Plasma Adiponectin (µg/ml)**

- BMI (kg/m²)

**P < 0.01**

*Circulation* 1999

- Circulation
- CAD
- nonCAD

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TNFα

IL-6

Leptin

Resistin

Adiponectin

BMI (kg/m²)

Plasma Adiponectin (µg/ml)
Adiponectin shows protective actions on obesity-linked metabolic and cardiovascular disease.

“healthy” adipocytes

Obesity → Adiponectin

WT   APN-KO

- High fat/sucrose → Insulin resistance
- ApoE → Atherosclerosis
- Ischemia-reperfusion
  - Shibata Nat Med 2005 → Acute myocardial infarction
- LAD occlusion
  - Shibata, Izumiya JMCC 2007 → Heart failure
- Pressure overload
  - Shibata Nat Med 2004 → Cardiac hypertrophy
- Chronic ischemia
  - Ouchi JBC 2004 → Vascular insufficiency
- High salt
  - Ohashi Hypertension 2006 → Hypertension
Preliminary studies:
Effects of resveratrol in WT and APN-KO mice fed a high calorie diet.

Treatment: Resveratrol
Mice: WT vs. APN-KO
Diet: High fat / high sucrose

Ouchi/Walsh - Metabolic measurements
Zang - Liver
Colucci - Cardiac function
Cohen - Angiogenesis
Changes in APN levels after treatment with RSV

Blood
WT
APN-KO (10 week-old)

Plasma APN levels

APN (µg/ml)

APN mRNA in fat

APN mRNA levels

RSV

WT

APN-KO

0
24 W

HF/HS

Sacrifice

Pre
24 wks

P<0.05

P<0.05

N.D
Effect of RSV on lipid accumulation in liver
Questions raised/potential new directions

1. Control of adiponectin release from fat (polyphenols, SIRT1, AMPK)

2. Adipokines: gene chip/proteomic analyses

3. Role of angiogenesis/hypoxia in fat on adiponectin release

4. Tissue effects of polyphenols (SIRT1, AMPK) Liver, Heart, Angiogenesis, ?, ?