CLA For Atherosclerosis and Diabetes Therapy: Opportunities, State of the Field and Future Research Directions

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CLA and Atherosclerosis: Therapeutic Opportunities

• Coronary heart disease, the consequence of atherosclerosis, is the single largest killer of women and men in the U.S.

• Prevalence of dyslipidemia (elevated LDL-C) very high
  – $\approx 64$ million Americans

• Treatment of low HDL-C is new therapeutic opportunity.
CLA and Diabetes: Therapeutic Opportunities

• Type II Diabetes Global Epidemic
  – Currently 150 million patients world-wide
  – Projections: 220 million by 2010
  – 300 million by 2025

• Incidence of Type II Diabetes closely linked to incidence of obesity
  – 300,000 obesity related deaths/year in US
Metabolic Syndrome/Syndrome X
(As Defined by NCEP ATP III)

Metabolic syndrome is linked to Insulin Resistance

Major Risk Factors
- smoking
- hypertension
- low HDL
- family history
- age
- obesity

Defined as any 3 of Following:
- Abdominal obesity ≥102 cm men or ≥88 cm women
- Triglycerides ≥150 mg/dL
- HDL-C <40 mg/dL men or <50 mg/dL women
- Blood pressure ≥130/ ≥85 mm Hg
- Fasting Glucose ≥110 mg/dL

Large Potential Patient Population
- 42 Million in US
CLA Anti-Obesity, Anti-Diabetic and Lipid Lowering Effects: Therapeutic Implications for Metabolic Syndrome

• In the last 2 years, several clinical studies have shown reduction in body fat with Tonalin® treatment

• Sustained reduction in body fat would have tremendous therapeutic benefit in human patients with insulin resistance.
  – Abdominal Obesity

• Metabolic Syndrome potentially large untreated patient population: 42 million US

• No universal reimbursement for obesity drugs, and metabolic syndrome is not currently an approvable indication
CLA and Atherosclerosis: State of the Field

- Dietary CLA lowers serum lipids in rodents

- CLA inhibits atherosclerotic plaque formation in rabbit and hamster models of experimental atherosclerosis
  - Total cholesterol and LDL-C lowered

- Limited human data show no effect on serum cholesterol and total lipids
  - CLA lowers HDL-C but not LDL-C
CLA and Atherosclerosis: Issues/Controversy

- Is the goal to prevent or treat atherosclerosis?
- Minimal published literature in physiologically relevant models
  - Most published data show lipid lowering
  - Minimal data on atherosclerotic plaque formation
- Very little human data
- Optimal Dose? Optimal Isomer Profile?
- Very limited mechanistic data in published literature
CLA and Atherosclerosis: Future Research Direction

• Examine underlying mechanisms for specific CLA isomers

• Expand the knowledge base for mechanistic effects of CLA beyond lipid lowering

• Examine ability of CLA to directly target cellular events leading to plaque formation/plaque instability
  – Inhibition of inflammatory events in the vessel wall
  – Enhancing plaque stability and/or reducing plaque rupture

• Embrace genomics technologies
  – CLA-induced pattern(s) of gene expression in relevant tissues
CLA and Diabetes: State of the Field

• Dietary CLA consumption prevents development of hyperglycemia in young male ZDF pre-diabetic rats
  Houseknecht et al. 1998 BBRC 244:678
  Ryder et al. 2001 Diabetes 50:1149

• Some but not all CLA effects mimicked by pair-feeding
  – GTT
  – Glucose transport (muscle)
  – Glycogen synthase
  – Gene expression
CLA and Diabetes: Issues/Controversy

• Only 2 papers in literature

• Rodent strain differences in anti-obesity and perhaps anti-diabetic/insulin resistance effects

• Diabetes prevention or treatment the goal?

• What is the relative importance of reduced feeding/fat mass to prevention of hyperglycemia?

• How important is lipid-lowering to the anti-diabetic effects?

• Mechanisms? Do CLA isomers activate PPARs?
Co-Activators

Pharmaceuticals

PPARγ

Ligand

RXR

Co-Repressors

Fatty Acid Metabolism

Transcription

PPRE

DNA

Adipocyte Differentiation

Insulin Action

Lipid Metabolism

Cancer

Inflammation/Immune Function

Houseknecht et al. 2002
Is it PPARα or PPARγ?

- PPARα -/- mice are protected from Insulin Resistance induced by High-Fat feeding

- PPARα -/- mice fed mixture of CLA isomers:
  - CLA-induced activation of PPARα in liver was abolished
  - CLA-induced changes in body composition are independent of PPARα
  - CLA induced expression of UCPs and genes involved in fatty acid oxidation and fatty acid transport in liver, muscle and adipose tissue, independent of PPARα
  - Serum triglycerides were lowered independent of PPARα

Guerre-Milo et al. 2001

Peters et al. 2001
Ligand Binding Domains of PPAR Are Large

Nolte et al. 1998 Nature
CLA and Diabetes: Issues/Controversy

- Only 2 published papers
- Rodent strain differences in anti-obesity and perhaps anti-diabetic/insulin resistance effects
- Diabetes prevention or treatment the goal?
- Relative importance of reduced feeding/fat mass to prevention of hyperglycemia?
- How important is lipid-lowering to the anti-diabetic effects?
- Mechanisms? Do CLA isomers activate PPARs?
- Effects of Specific Isomers?
- Optimal Dose? Safety? Tolerance?
- Are serum CLA concentrations important? What is the optimal “PK” profile in serum, tissues?
CLA and Diabetes: Future Research Direction

• Mechanistic effects of specific CLA isomers on pre-diabetic and diabetic models/populations
  – Pancreas and liver focus for pre-diabetic
• PPAR binding and functional selectivity of CLA isomers
• Dose escalation and “PK” experiments
• Safety and toleration for chronic dosing
• Efficacy of CLA in polypharmacy
  – Insulin, glucose lowering agents, insulin sensitizers
  – Appropriate controls for clinical studies
• Diabetic control pre-screening and biomarker endpoint(s)
  – Hba1c