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
  - ≈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

Large Potential Patient Population

- 42 Million in US

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

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 of 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

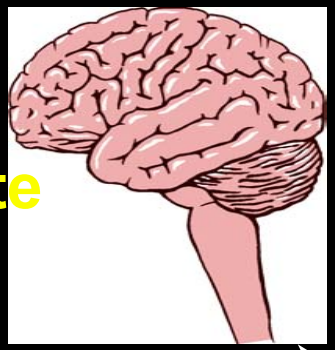
CLA and Diabetes: State of the Field

- **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 mimiced by pair-feeding**
  - **GTT**
  - **Glucose transport (muscle)**
  - **Glycogen synthase**
  - **Gene expression**



↑↓ Appetite

Brain

PPARγ

Adipocyte

↑↓ a P2/differentiation

↑↓ UCP2

↓ Size

↓ Leptin

↓ TNFα

→ Glut4/Transport

→ Glut4

↑ Glucose Transport

↑ UCP2

CLA

? Lipotoxicity

? Insulin Secretion

Pancreas

Skeletal Muscle

PPARα

↓ Lipid Content

↓ Plasma TG & NEFA

↑ Size

Liver

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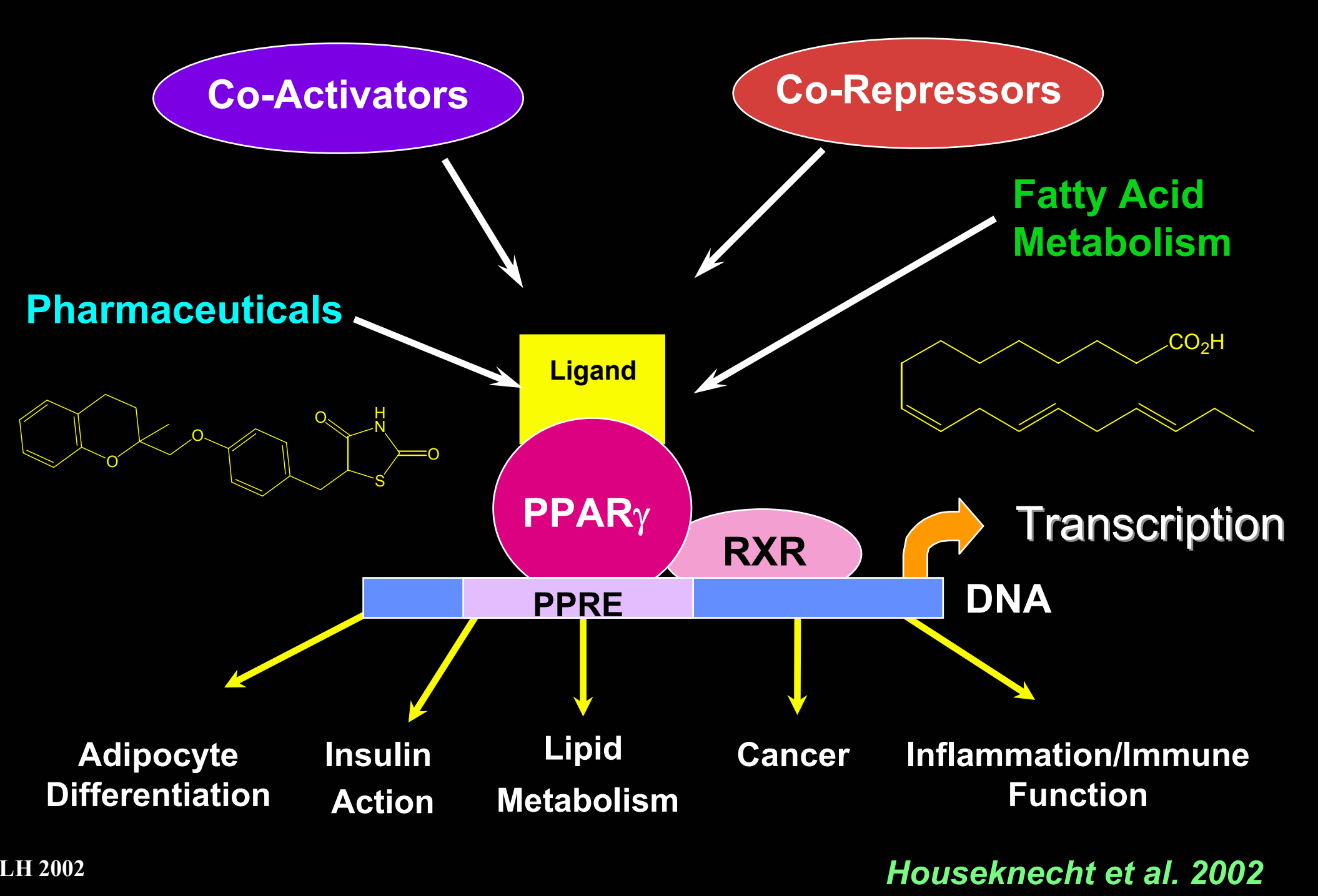
CLA and Diabetes: Issues/Controversy

- 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?



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Houseknecht et al. 2002

Is it PPARα or PPARγ ?

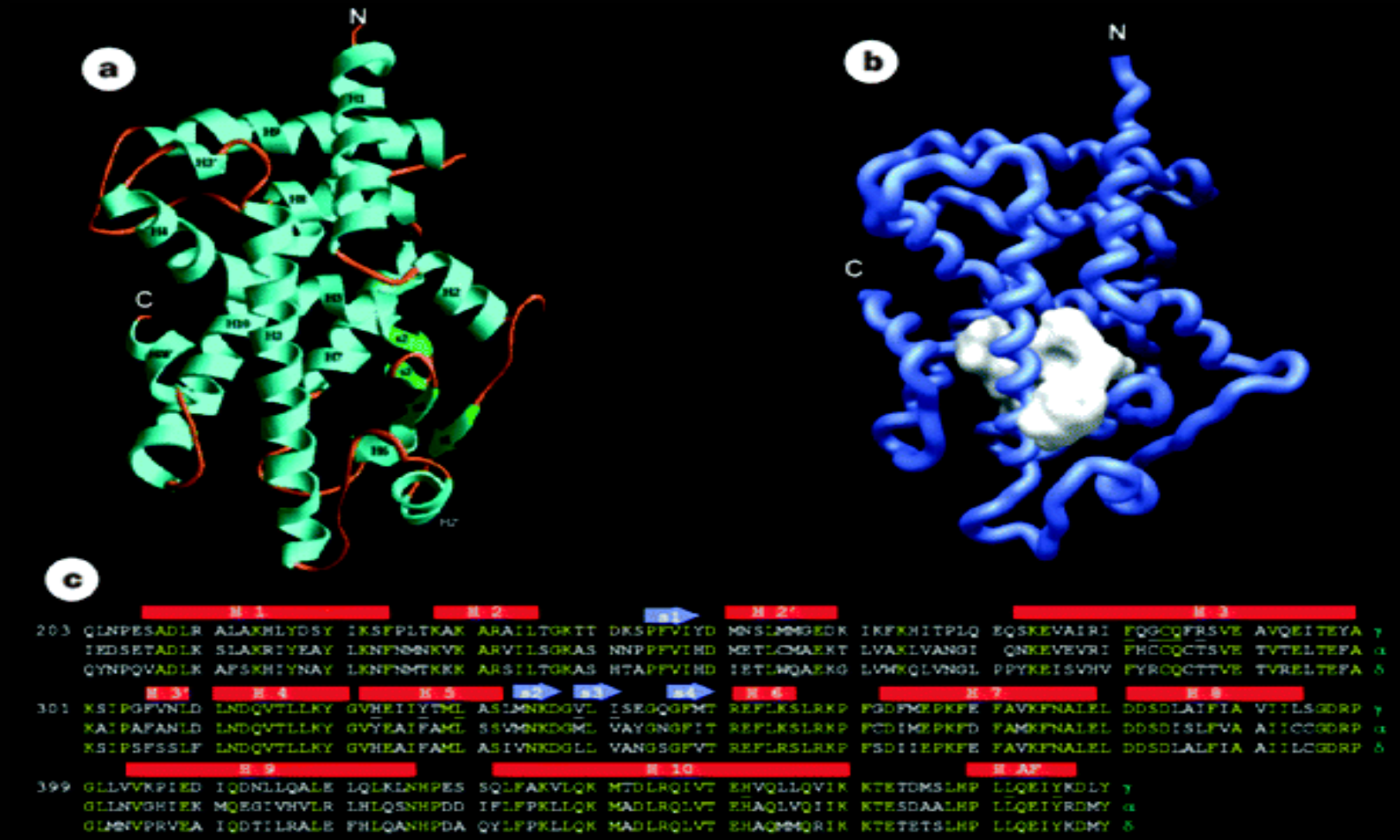
- **PPARα -/- mice are protected from Insulin Resistance induced by High-Fat feeding**

Guerre-Milo et al. 2001

- **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**

Peters et al. 2001

Ligand Binding Domains of PPAR Are Large



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Nolte et al. 1998 Nature

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- 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? Toleration?
- 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 escallation 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