Pilot Study: Conjugated Linoleic Acid Reduces Fasting Blood Glucose and Is Inversely Correlated with Leptin in Subjects with Type 2 Diabetes Mellitus

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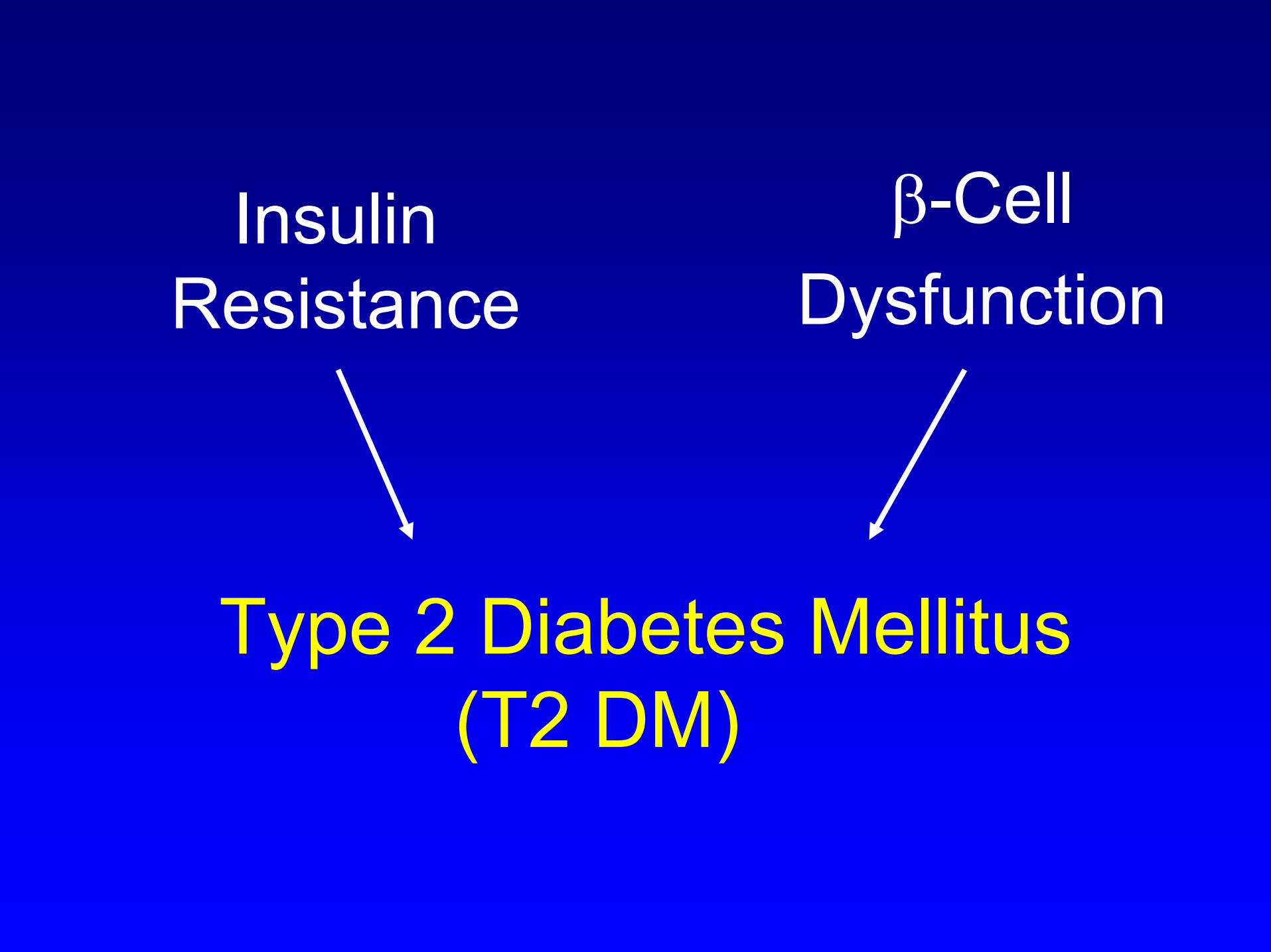
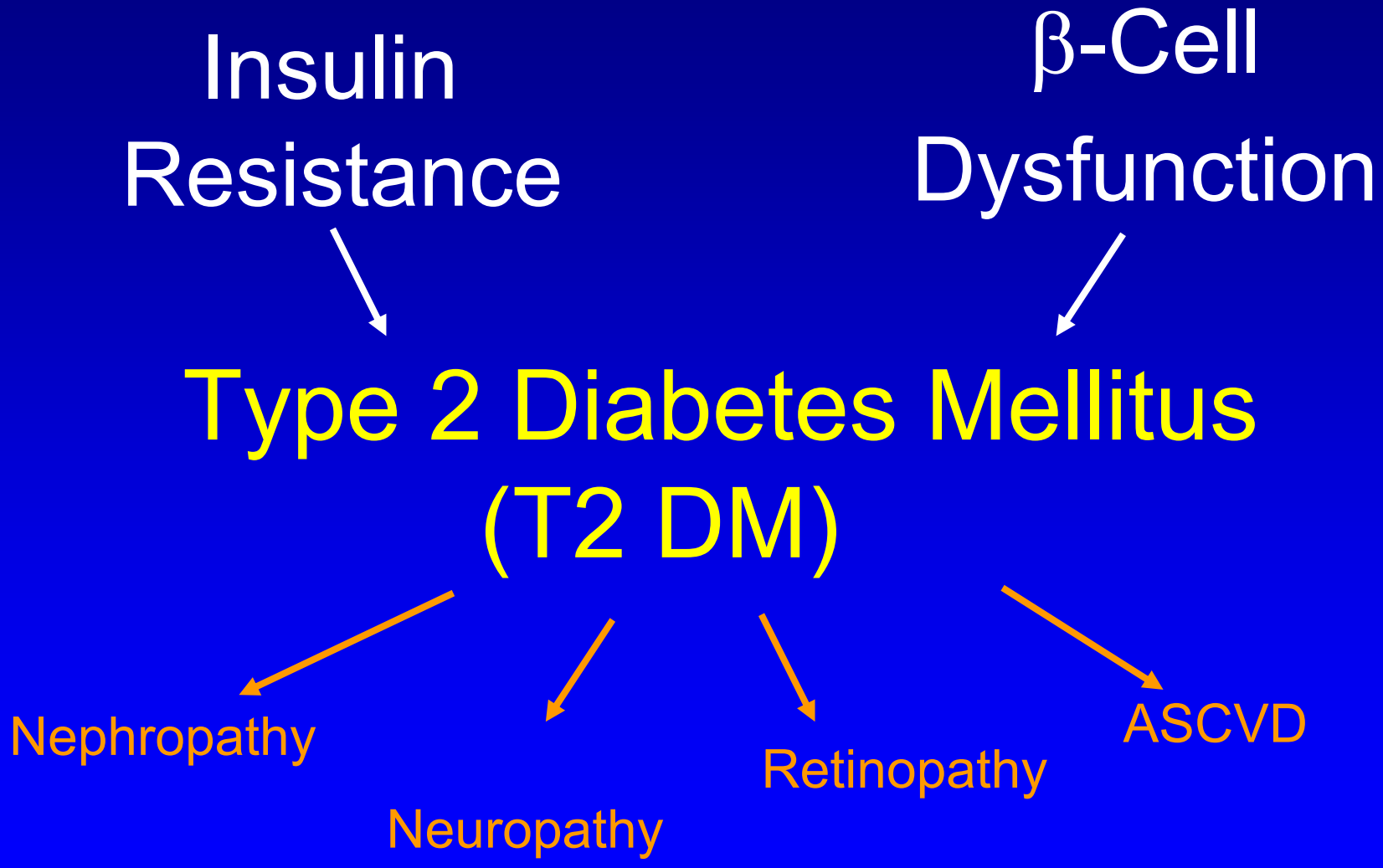

Insulin Resistance
β-Cell Dysfunction
Type 2 Diabetes Mellitus (T2 DM)


Insulin Resistance
β-Cell Dysfunction
Type 2 Diabetes Mellitus (T2 DM)
Nephropathy
Neuropathy
Retinopathy
ASCVD

Prevalence of Type 2 DM in the U.S.

- Sixth leading cause of death
- 17 million or (6%) have Type 2 DM
- Another 7% Americans Exhibit Impaired Fasting Glucose (IFG)
- 6 million Americans remain undiagnosed
- 50% have complications by time of dx
- Average duration of Type 2 DM = 7 years before dx
- 80-90% will need medication eventually
- 48% will require insulin

Costs of Type 2 DM

- $ 98 Billion lost per year from loss of productivity
- $ 44 Billion lost to direct costs of medical care

Management of T2 DM

- Diet
- Exercise
- Medication
- Exogenous Insulin Therapy

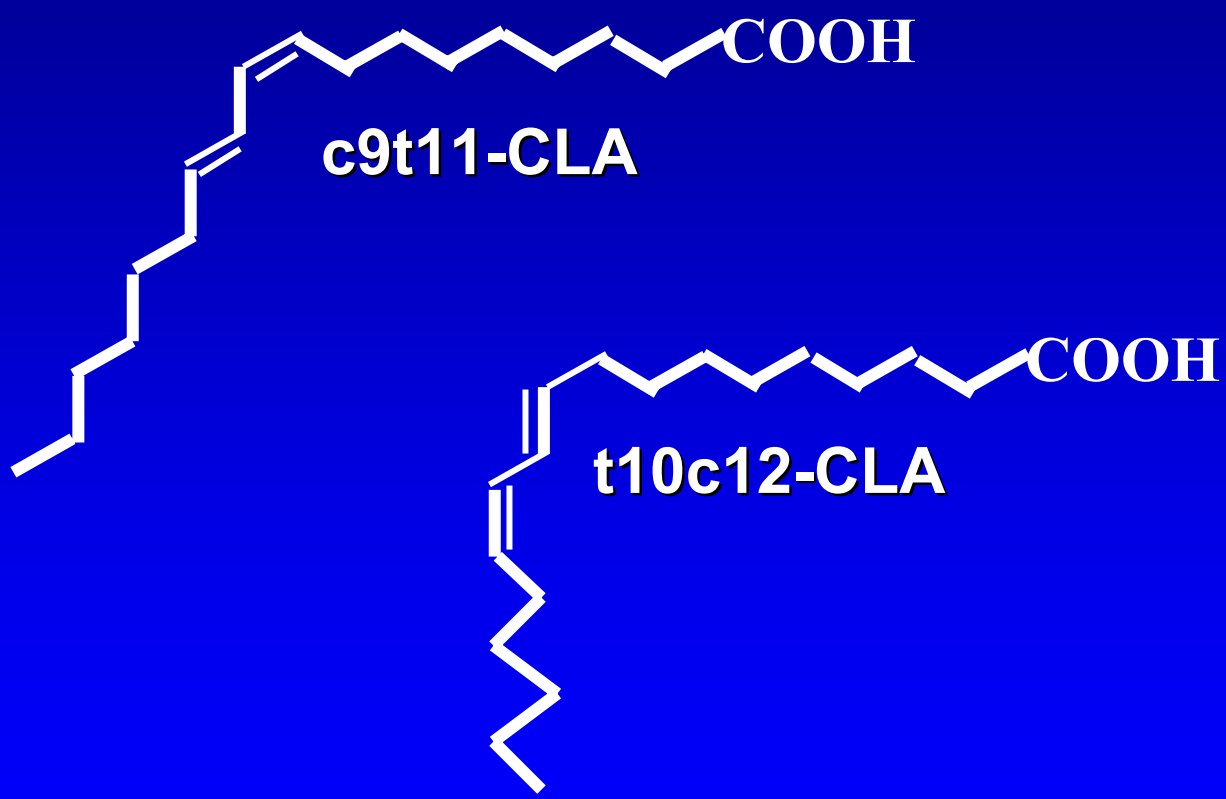
↓ Adiposity
↑ Insulin Sensitivity
and/or
↑ Insulin Output

Role of Dietary Fats in T2 DM

- Oleic acid may aid in management of glucose and insulin metabolism
  - Christiansen et al., 1997, others
- Some PUFAs may aid in management of dyslipidemias associated with T2 DM
  - Friedberg et al., 1998

➢ *Am Diabetes Assn (2002)*: Reduce saturated fats to less than 10% calories

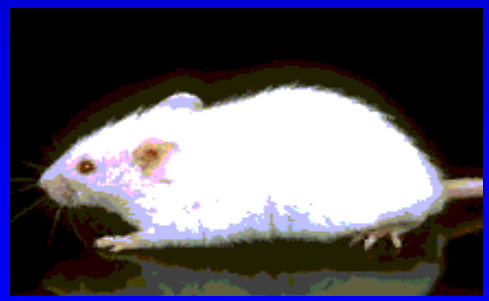
Conjugated Linoleic Acid



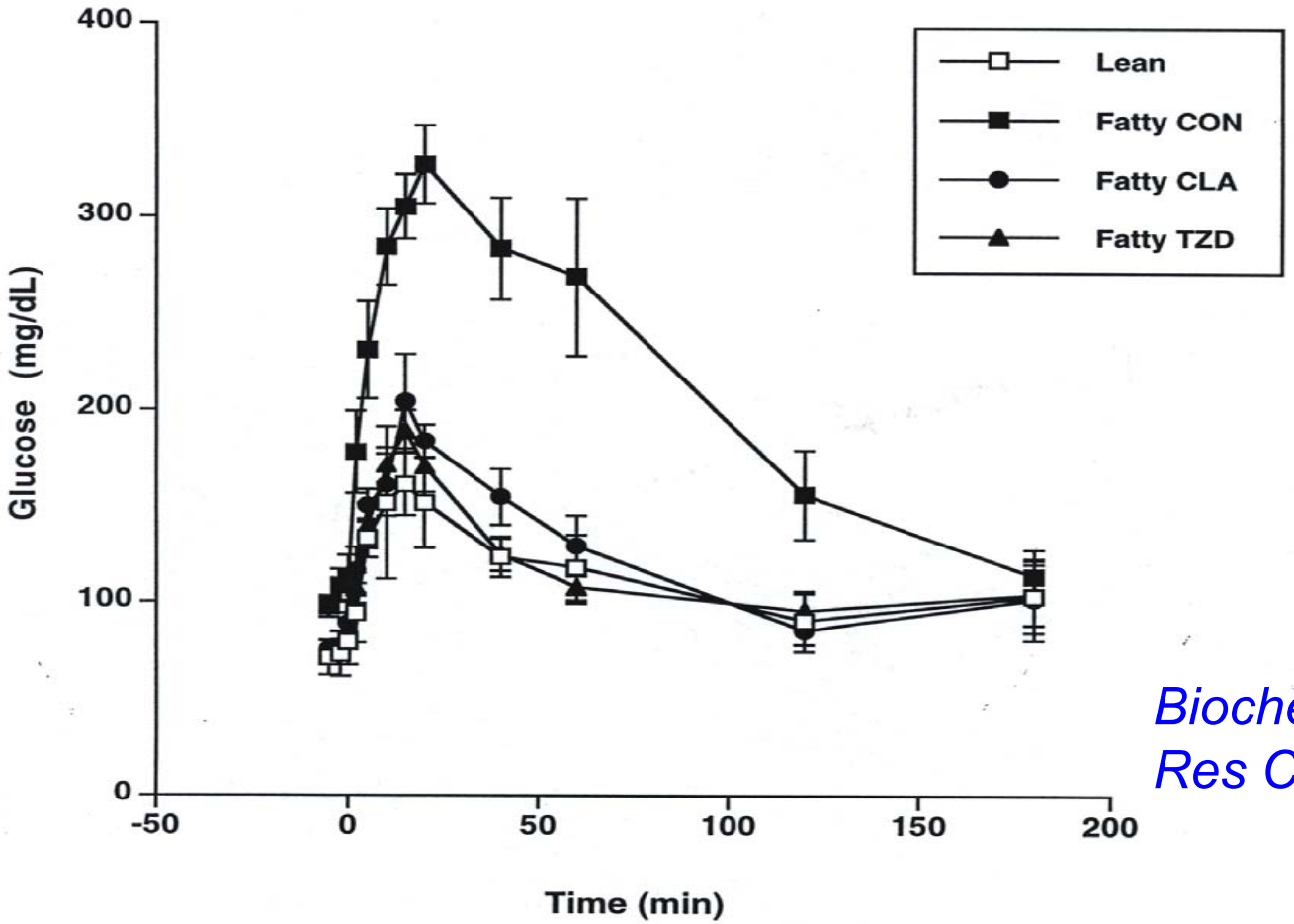
CLA Delays the Onset of Type 2 Diabetes in ZDF Rats

- ZDF Males, Diets : CON, 1.5% CLA, or TZD Diet
- 2 Weeks

***Biochem Biophys Res Comm* 244: 678-682 (1998)**
& M.A. Belury, unpublished data
& Ryder et al., (*Diabetes* 2001)



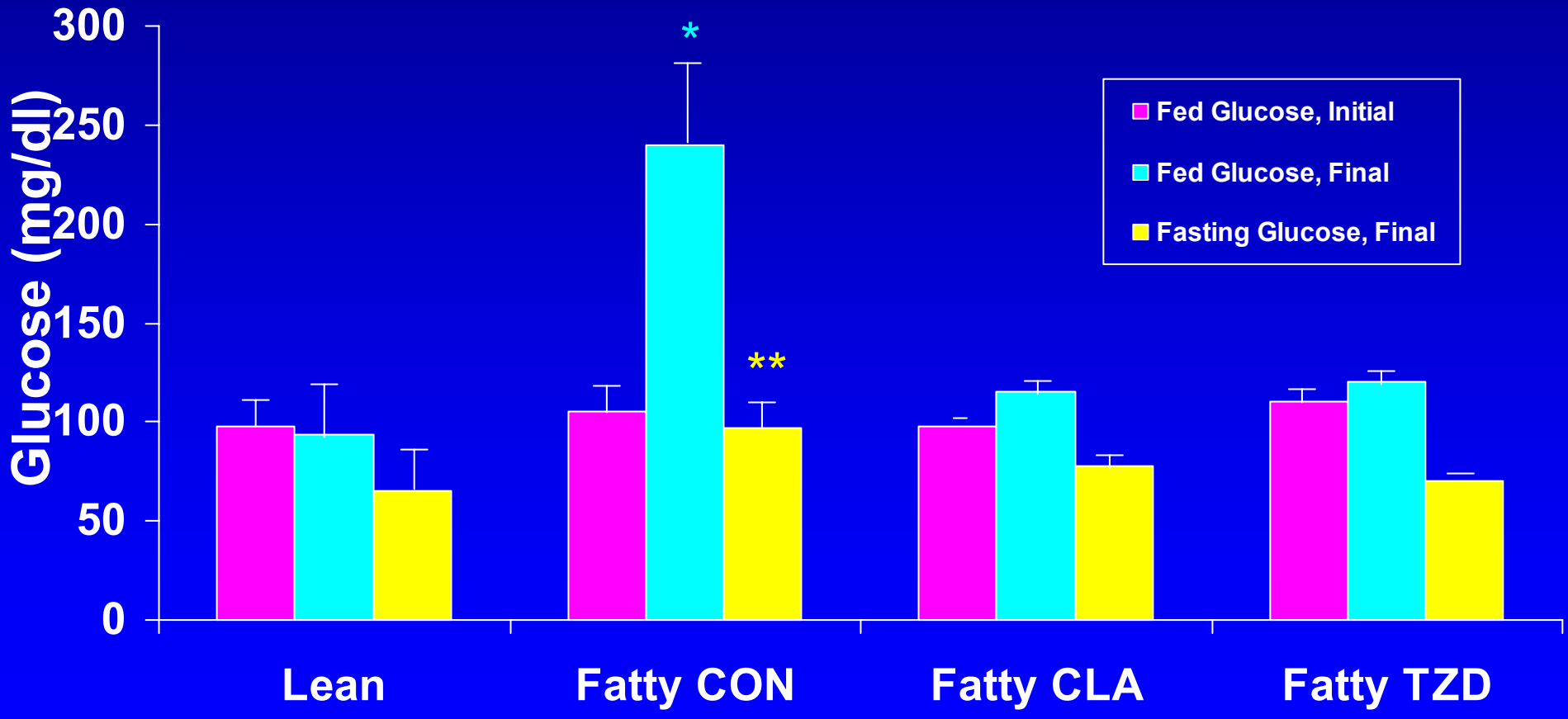
CLA Mixture Normalizes Impaired OGTT in ZDF Rats



Biochem Biophys Res Comm (1998)

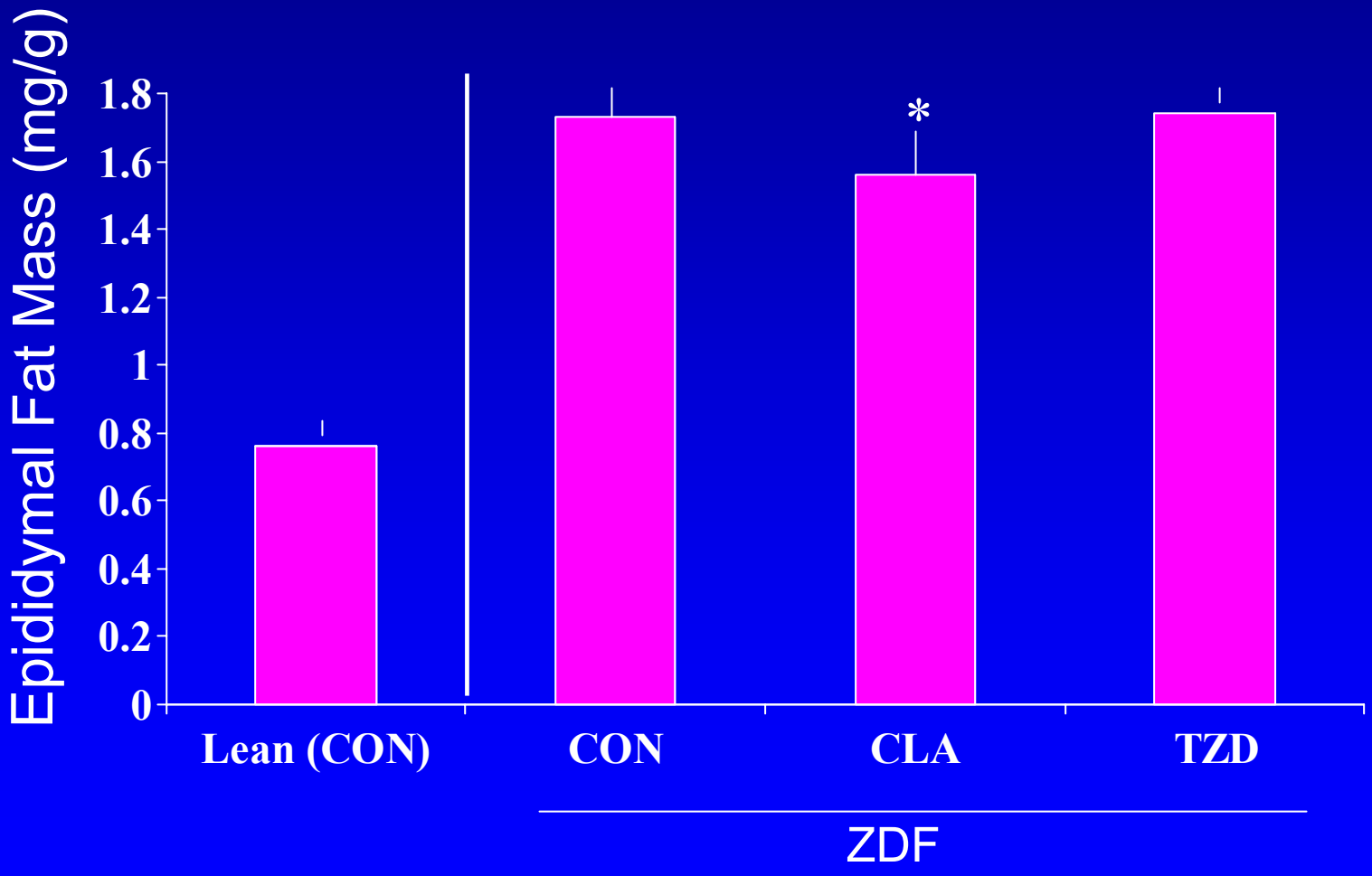
Effect of Dietary CLA on Glucose

Biochem Biophys Res Comm 1998

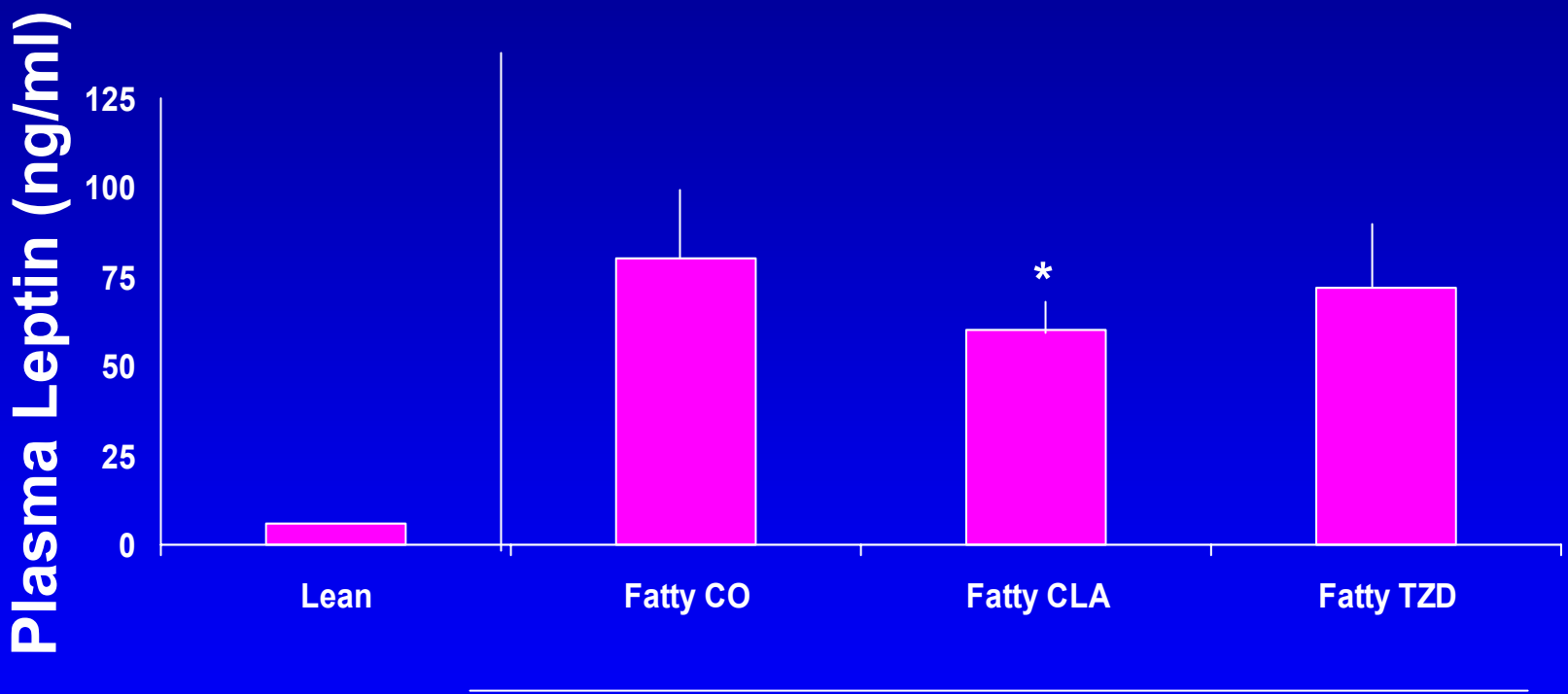


CLA Reduces Epididymal Fat Mass

Biochem Biophys Res Comm 1998



CLA Reduces Plasma Leptin



Belury and Vanden Heuvel, 1999

CLA and TZD: ZDF vs. Lean Littermates

Group	Liver Index (mg/g)	Hepatic Lipids (mg/g liver)	Epididymal Mass (mg/g)
L-CON	3.9 ± 0.2	24.7 ± 2.0	0.7± 0.1
L-CLA	4.3 ± 0.1 *	21.6 ± 4.4	0.6± 0.1 *
L-TZD	4.1 ± 0.3	20.9 ± 0.8	0.9± 0.2
D-CON	4.8 ± 0.2	63.1 ± 19.62	1.7± 0.1
D-CLA	4.8 ± 0.3	47.0 ± 4.94 #	1.6± 0.1 #
D- TZD	4.1 ± 0.1 #	34.7 ± 8.2 ##	1.7 ± 0.1

M.A.Belury, unpublished

Elucidate the relationship of CLA to improvements in the management of Type 2 diabetes mellitus

Subjects and Methods

- ✓ Subjects: Type 2 diabetes --- *no medication* for glucose control
- ✓ Block randomization
- ✓ Double-blind; CLA supplements (6.0 g / day) vs. safflower placebo, 8 weeks
- ✓ 3-Day Diet and Activity Records &

  24-Hr Recalls (0, 2, 4, 6, 8 wk)
- ✓ Before (Wk 0) vs. During CLA (Wk 8)
  - Anthropometry
  - Blood glucose, Insulin and Leptin
  - Fatty acid composition

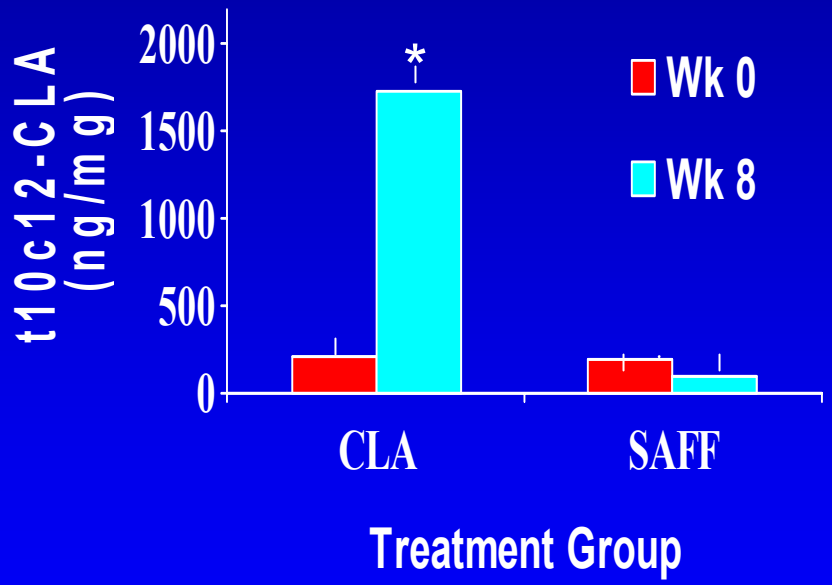
Subject Characteristics

	CLA	Placebo
N	11	10
Gender (M/F)	5/6	6/4
Age (Yrs)	55 ± 14	62 ± 13
FPG (mg/dl)	146 ± 38	134 ± 34
Body Weight	206 + 47	173 + 42

M.A.Belury, unpublished

Supplement Compliance

- Reported compliance
  80% minimum
- t10c12-CLA as Marker of Compliance
  (* P<0.05)

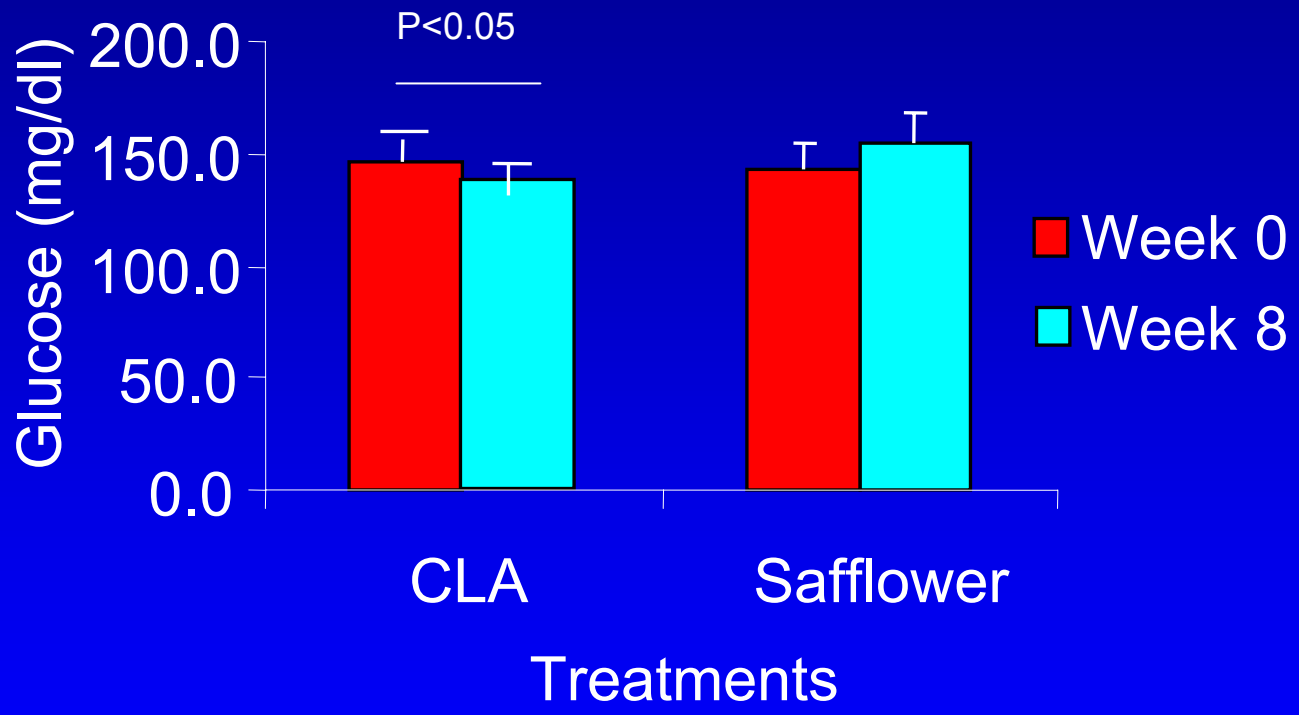


M.A.Belury, unpublished

Objective 1:

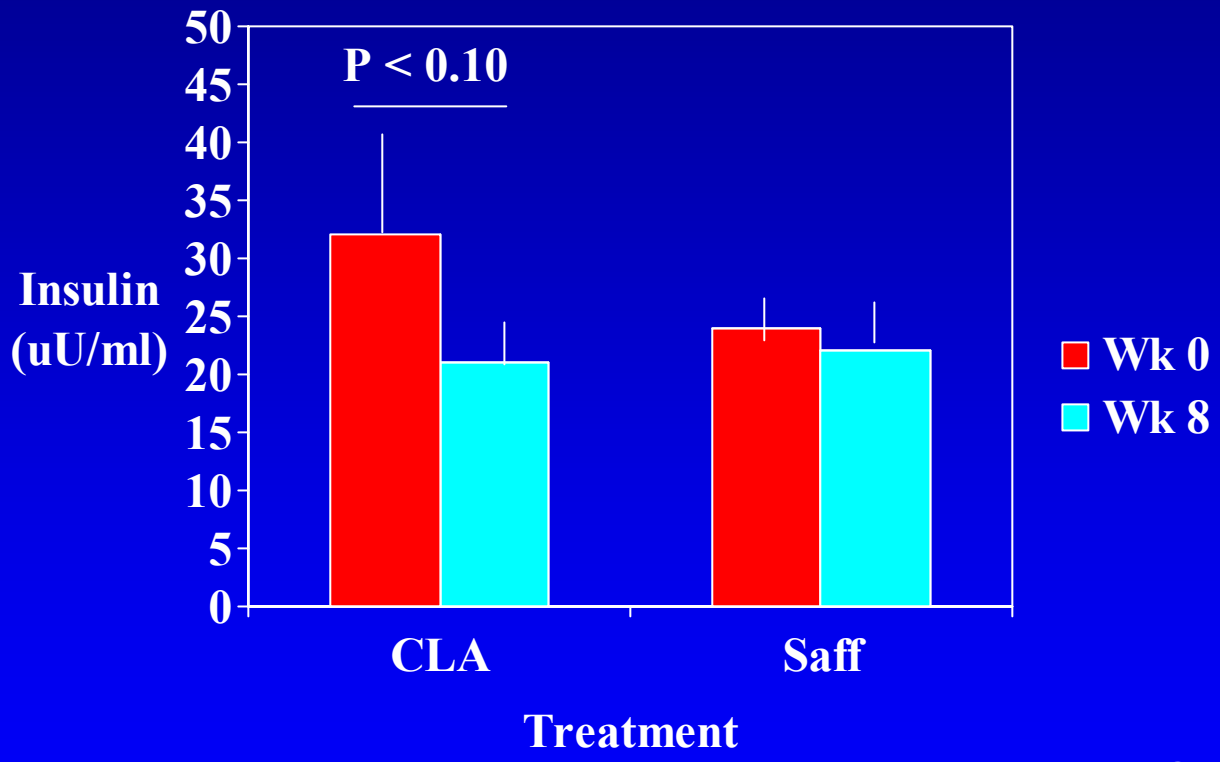
To determine the effects of supplemental CLA on fasting blood glucose (FBG), insulin, body weight and leptin in subjects with Type 2 DM

CLA Lowers Fasting Blood Glucose



M.A.Belury, unpublished

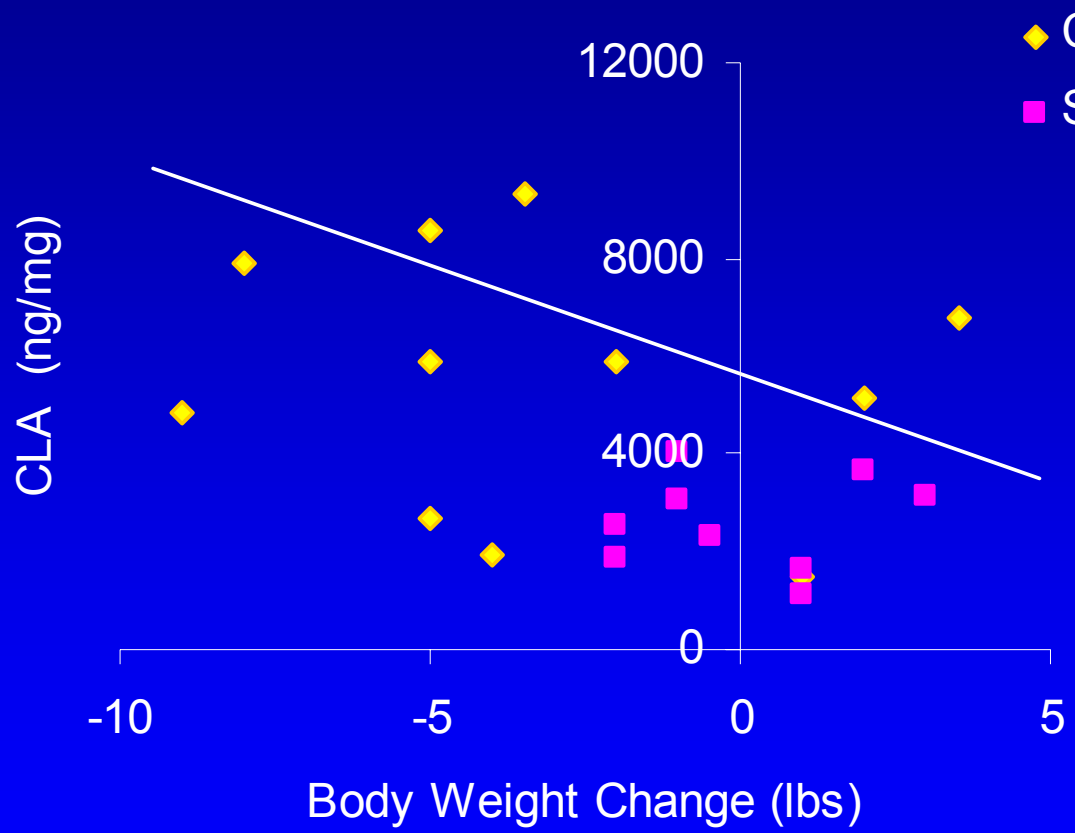
Effect of CLA on Fasting Insulin



M.A.Belury, unpublished

P <0.05 CLA (Wk 0) vs. Saff (Wk 0)

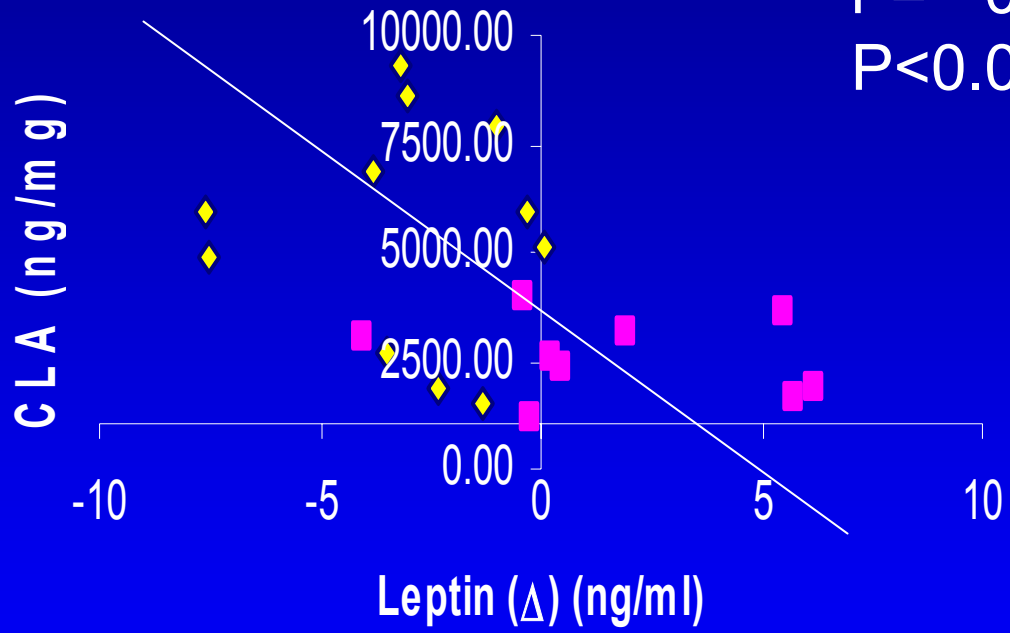
Correlation of Plasma CLA and Weight Reduction (Wt Δ)



r = - 0.3739
P<0.100

M.A.Belury, unpublished

Negative Correlation Between Plasma CLA vs. Serum Leptin (Δ)



M.A.Belury, unpublished

Biological Activities of c9t11-CLA vs. t10c12-CLA (Synthetic Mixture of CLA) May Differ

Isomeric Content (%CLA) of Selected Foods vs. Synthetic Mix

	c9t11	7,9 (c/t) 8,10 (c/t)	t10c12-CLA, Others
Beef[a]	74.8	15.8	9.0
Cheese[b]	82.6	8.3	9.0
CLA Mix	48.7	----	51.3

[a] Yurawecz et al., 1998

[b] Sehat et al., 1998

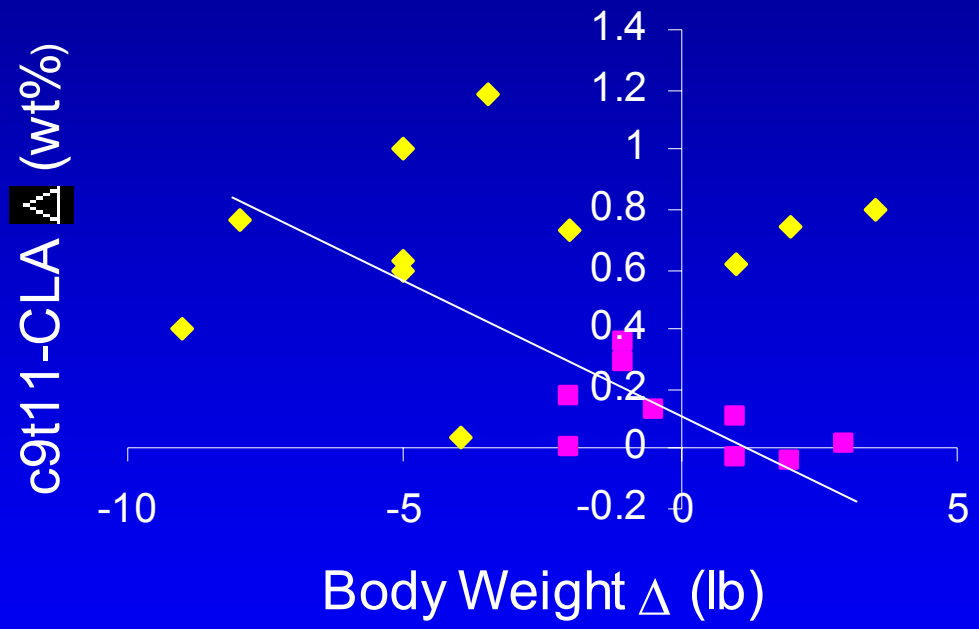
Some Biological Activities of c9t11- CLA

- Accumulates extensively in tissues (Belury et al., 1997, Ip et al., 1999, Banni and Belury, unpub.)
- Alters gene expression & affects tissue development (Moya-Camarena et al., 1999, others)
- Inhibits mammary carcinogenesis (Ip et al., 2002)

Objective 2:

To determine the relationship of the serum level of the dietary isomer of CLA, rumenic acid (c9t11-CLA), with body weight and leptin in subjects with Type 2 DM

c9t11-CLA (Δ) vs. Body Weight (Δ)

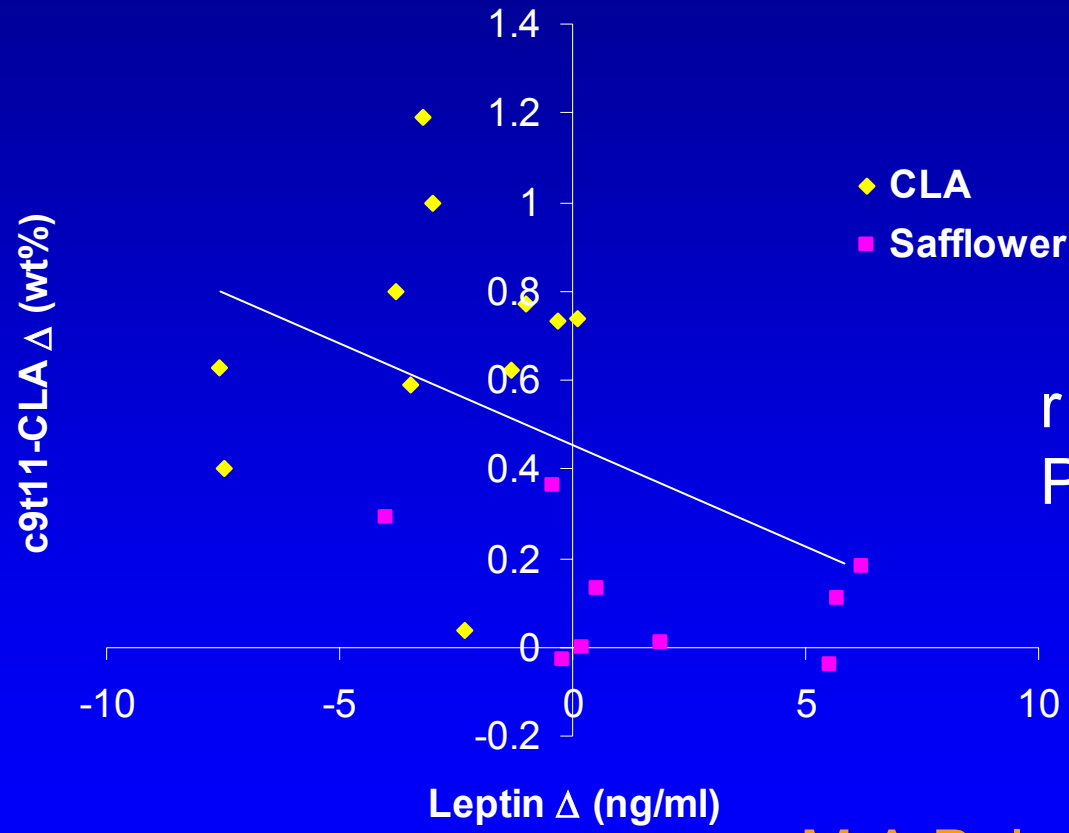


R = - 0.3230
P <0.20

◆ CLA
■ Safflower

M.A.Belury, unpublished

c9t11-CLA (Δ) vs. Leptin (Δ)



r = - 0.3961
P< 0.100

M.A.Belury, unpublished

Objective 3:

To determine the extent that CLA may act through a mechanism involving peroxisome proliferator-activated receptor-γ (PPARγ)

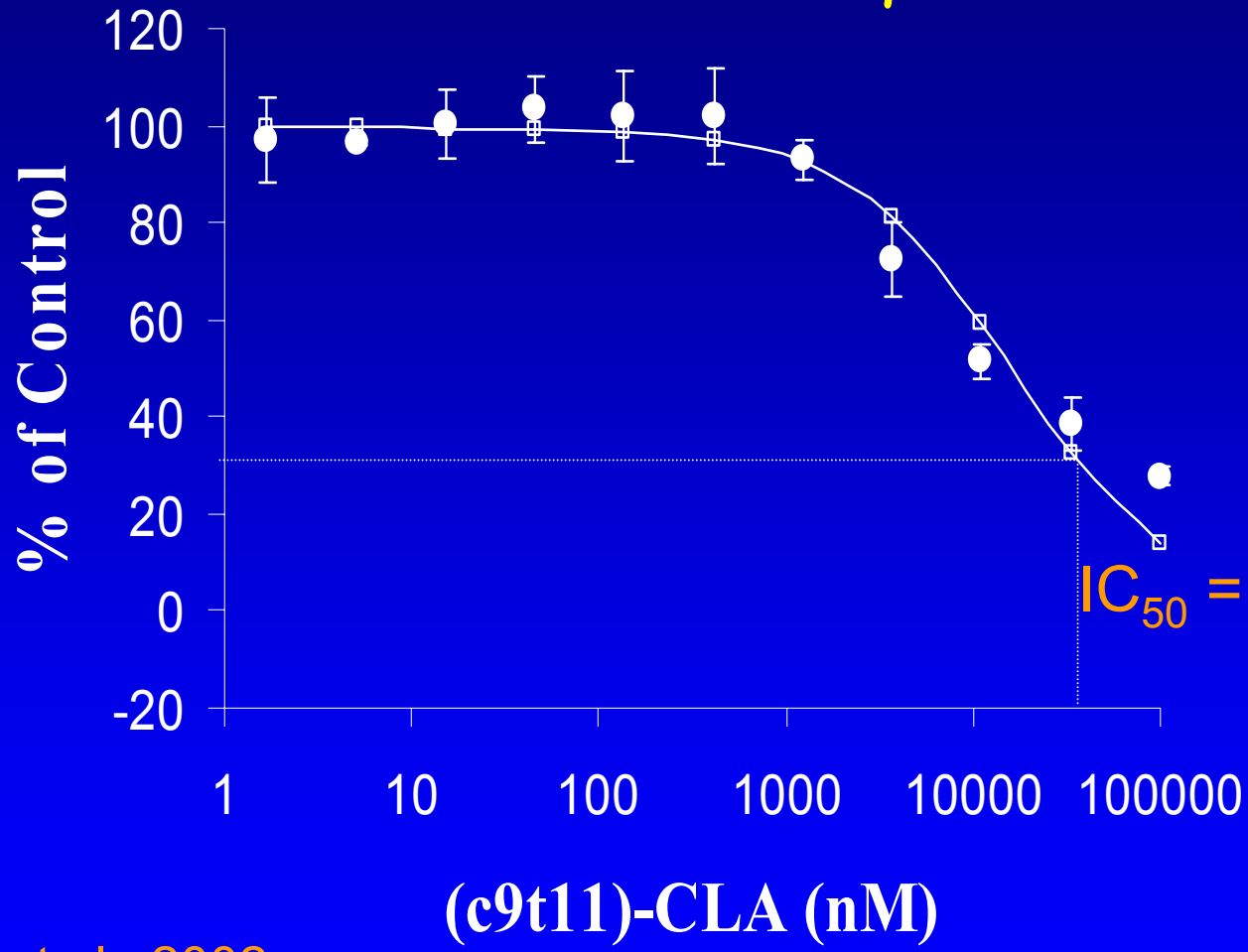
Distribution of PPARs

- PPARα: liver, heart, kidney, muscle
- PPARβ: ubiquitous
- PPARγ1: adipose tissue, colon, breast epithelium, macrophages, prostate, muscle
- PPARγ2: Adipogenesis

PPAR as a Transcription Factor

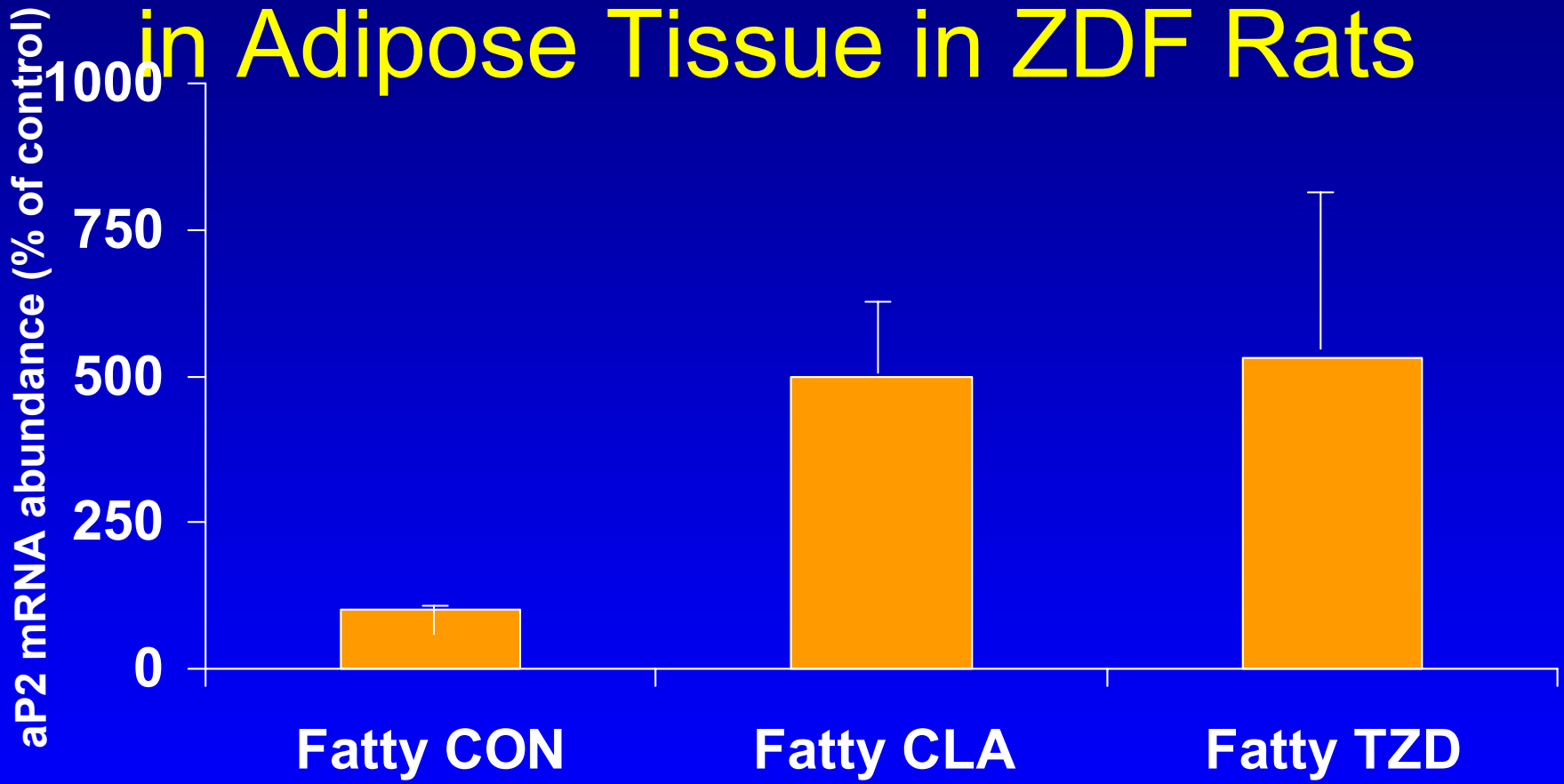
- Requires **Ligand**
- Associates with PPAR Response Element (**PPRE**); DR-1
- Heterodimerizes with **RXR** (requires 9-cis RA)
- Some **Responsive Genes** Include
  - FABPs (ap2), Acyl-CoA Oxidase, CYP4A, LPL, negative – ApoCIII

Binding Affinity of c9t11-CLA for LBD of h-PPARγ



Belury et al., 2002

Dietary CLA Induces aP2 mRNA in Adipose Tissue in ZDF Rats



Biochem Biophys Res Comm 1998

Is the Improvement of Fasting Blood Glucose in T2 DM Regulated by Activation of PPARγ?

Is the Improvement of FBG in T2 DM Regulated by Activation of PPARγ?

Could improvement of FBG be due to downstream metabolites of CLA?

CLA Metabolites

octadecadienoate (c9,t11 or t10c12)

↓ Δ6 desaturase *

octadecatrienoate (c6,c9,t11 or c6t10c12)

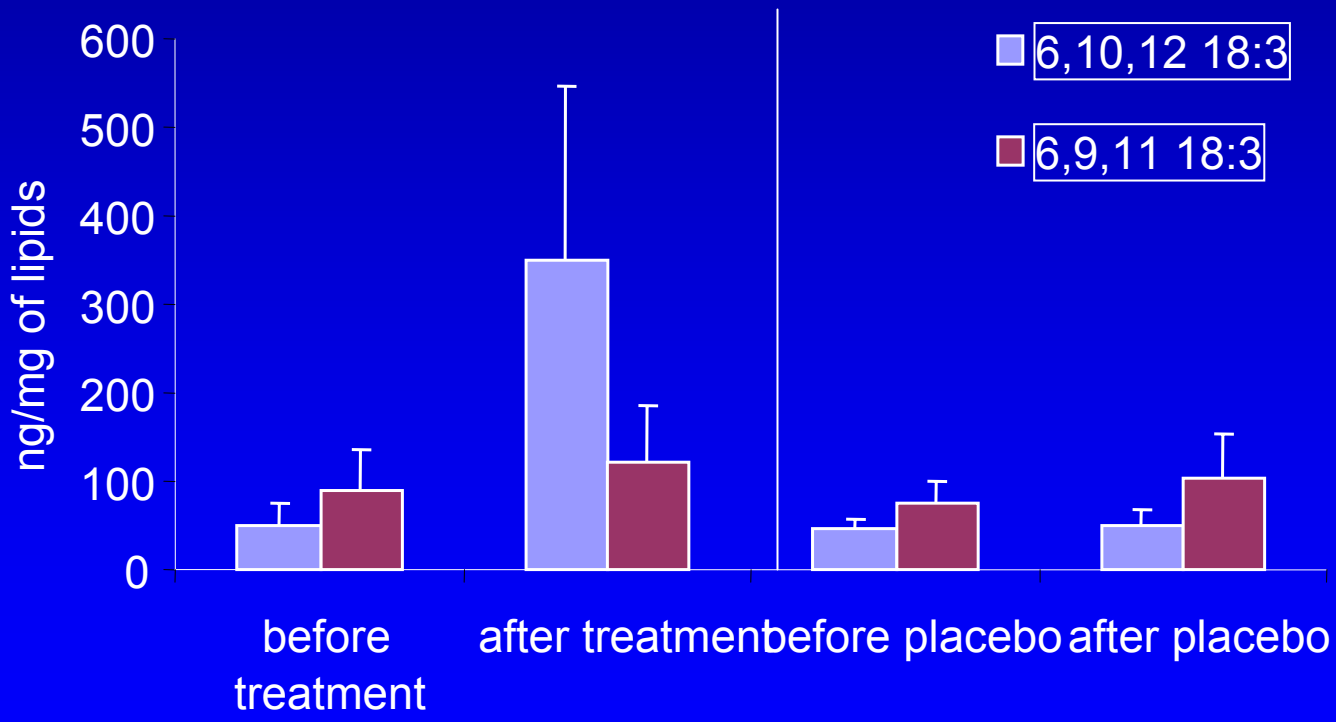
↓ elongase

eicosatrienoate (c8,c11,t13 or c8t12c13)

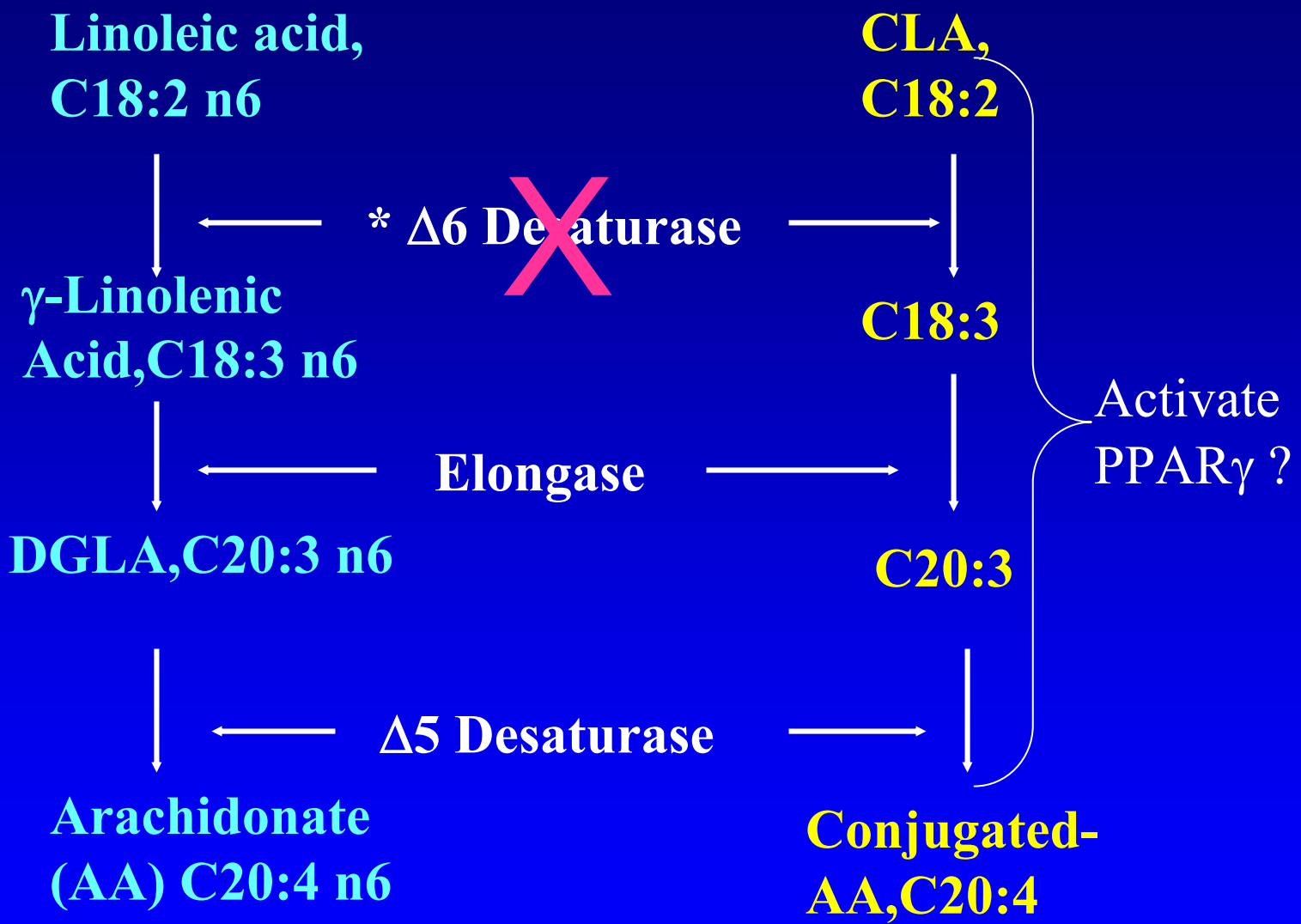
↓ Δ5 desaturase

eicosatetraenoate (c5,c8,c11,t13 or c5c8t12c14)

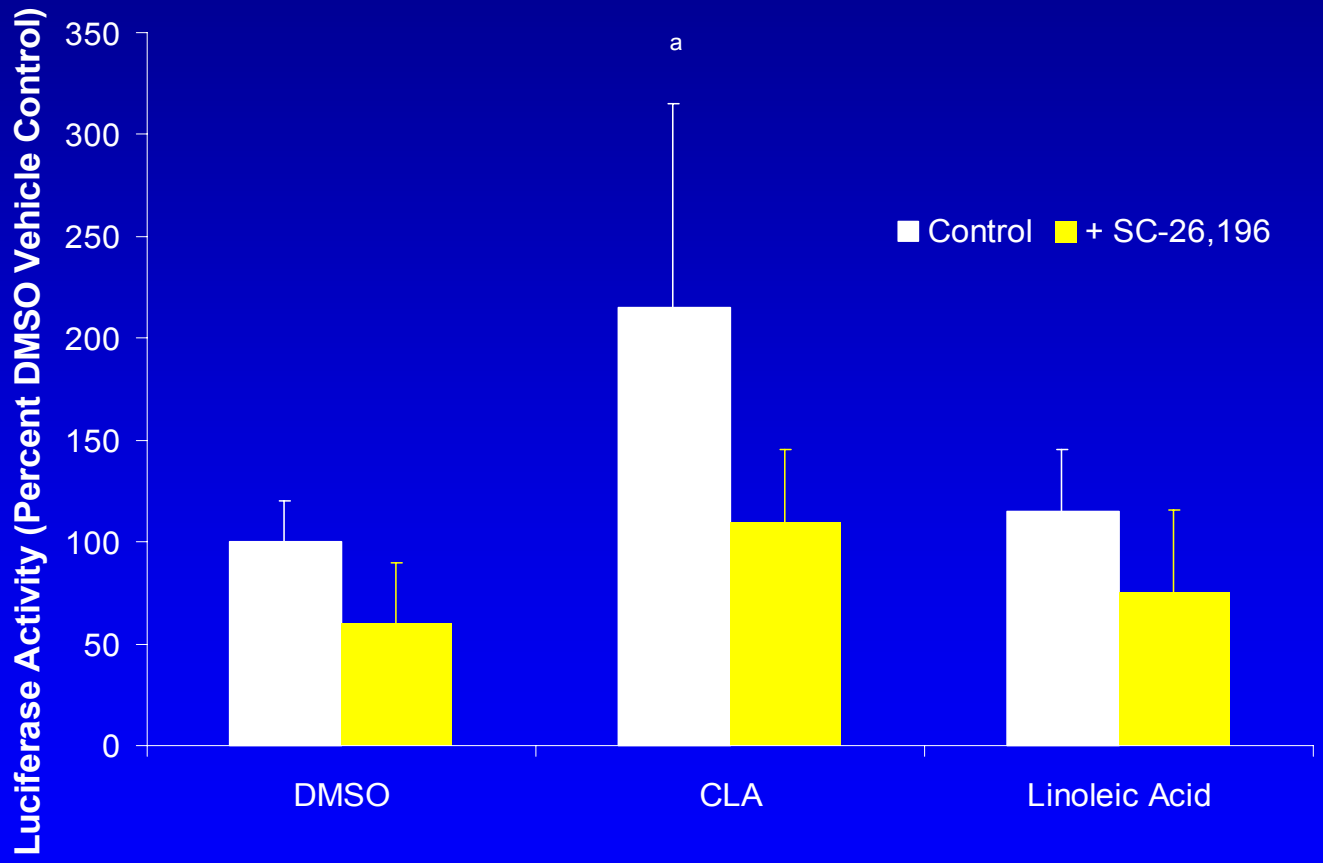
CD 18:3 Isomers in Subjects with T2 DM



M.A.Belury, unpublished


Linoleic acid,
C18:2 n6
CLA,
C18:2
* Δ6 Desaturase
γ-Linolenic
Acid,C18:3 n6
C18:3
Activate
PPARγ ?
Elongase
DGLA,C20:3 n6
C20:3
Δ5 Desaturase
Arachidonate
(AA) C20:4 n6
Conjugated-
AA,C20:4

Inhibiting Δ6 Desaturase Reduces Activation of PPARγ



Belury et al., 2002

Summary: CLA and Diabetes

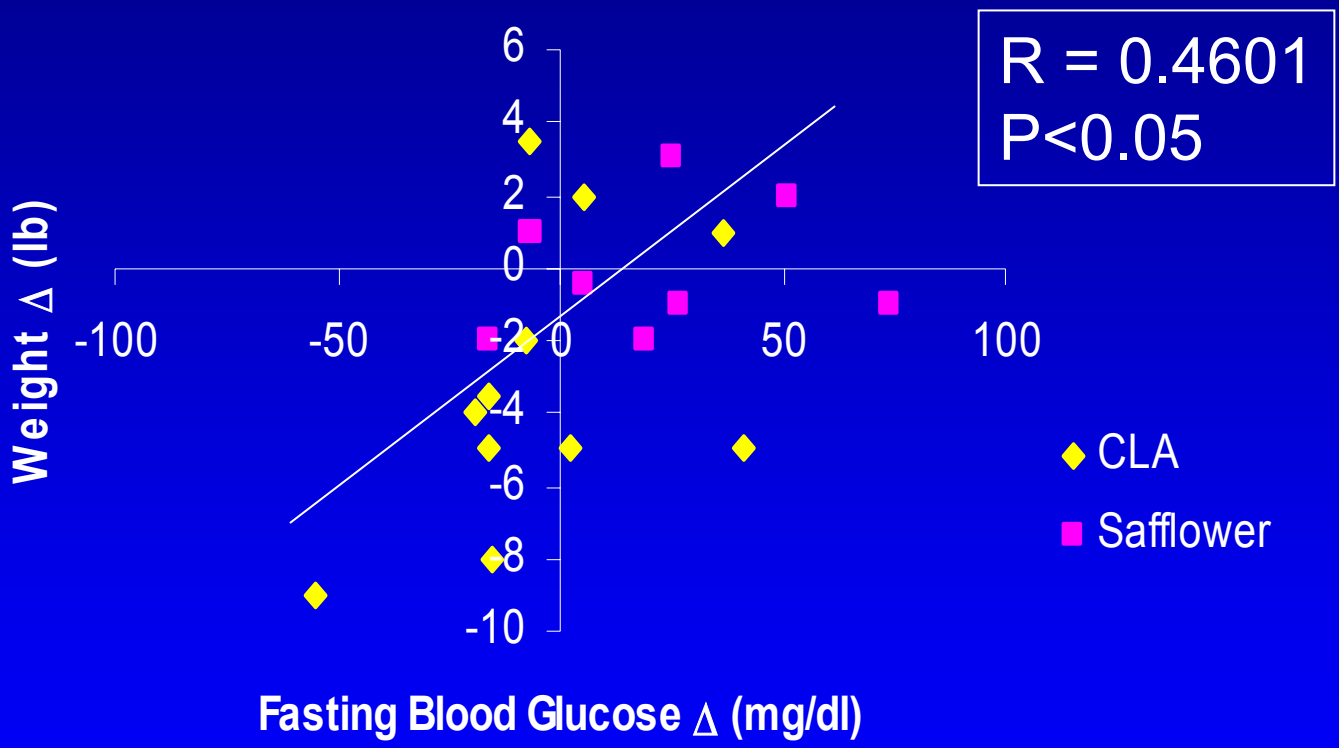
CLA Supplementation in Subjects with T2 DM:

- Significantly reduced ($p < 0.05$) FBG
- Fasting insulin & insulin sensitivity ??

Summary: CLA and Weight Regulation

- Correlation coefficients
  - CLA vs. Body weight ($r = -0.3739$; $P < 0.10$)
  - CLA vs. Leptin ($r = -0.4349$; $P < 0.05$)
- c9t11-CLA weaker inverse correlations with body weight and leptin than total CLA

Improved FBG correlates with Reduced Body Weight



M.A.Belury, unpublished

Summary: CLA and Weight Regulation

- Inversely correlations
  - CLA vs. Body weight ($P<0.10$)
  - CLA vs. Leptin ($P<0.05$)
- c9t11-CLA weaker inverse correlations with body weight and leptin than total CLA

Some Biological Activities of t10c12- CLA

- Readily forms metabolites in humans (Banni and Belury, unpublished data)
- Alters gene expression (SCD, hr-lipase, others)
- Reduces adiposity in experimental animals (Park et al., 2000)

Conclusions

- CLA may improve FBG via improved insulin sensitivity, body composition and/or leptin levels
- Effect of CLA on leptin suggests a role for adipose tissue in CLA's effects on FBG
- Isomeric specific effects of t10c12-CLA and c9t11-CLA in regulating FBG and body weight are likely

Future Directions

- Size (N) and duration
- Adipose tissue composition & distribution using MRI
- Isomer & metabolite activity
- Leptin and other hormones involved in food intake
- Mechanism(s) of action at tissue an molecular levels

Acknowledgments

- Annie Mahon, M.S., R.D.
- Leslie Borhmann, M.S.
- Lingling Shi, M.S.
- Ania Kempa-Steczko
- YuHuan Gu, Ph.D.
- Sebastiano Banni, Ph.D.
- Karen Houseknecht, Ph.D.
- Jack Vanden Heuvel, Ph.D.

Pharmanutrients & Natural

National Cattleman's Beef Assn