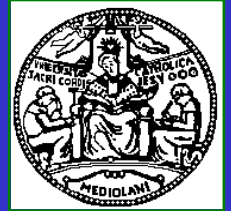


# Carnitine: The Science Behind an Essential Nutrient

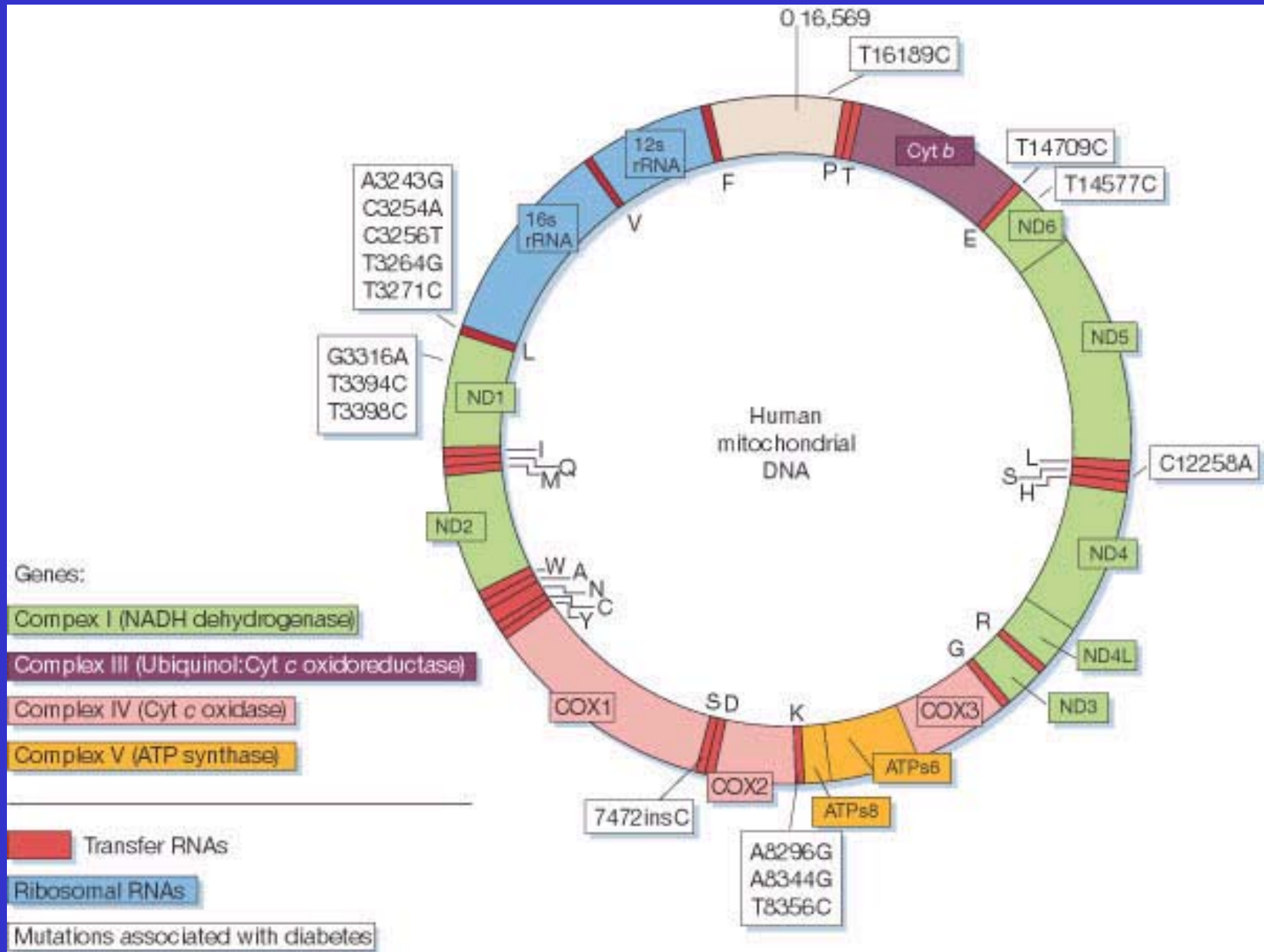
**GELTRUDE MINGRONE, MD, PHD  
CATHOLIC UNIVERSITY, ROME, ITALY**



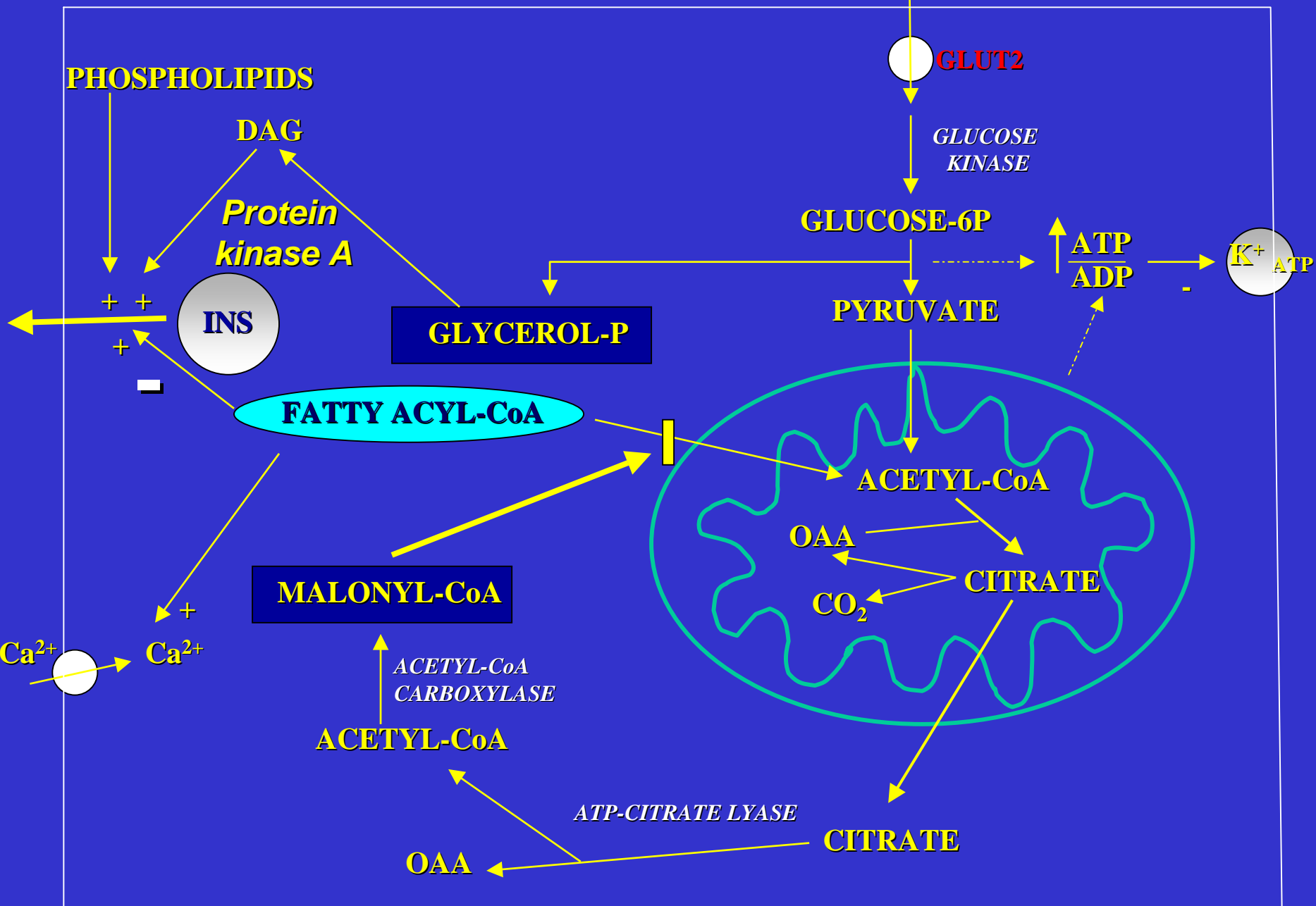
**MITOCHONDRIAL DIABETES**  **1-2% of all cases of DM**

★ **Impaired glucose-induced insulin secretion**

★ **Reduced oxidative phosphorylation (reduced O<sub>2</sub> consumption)**



# GLUCOSE





**A cellular model of MODY3 expressing dominant-negative Hepatic Nuclear F-1 $\alpha$  also displayed deletion of glucose-induced insulin secretion**

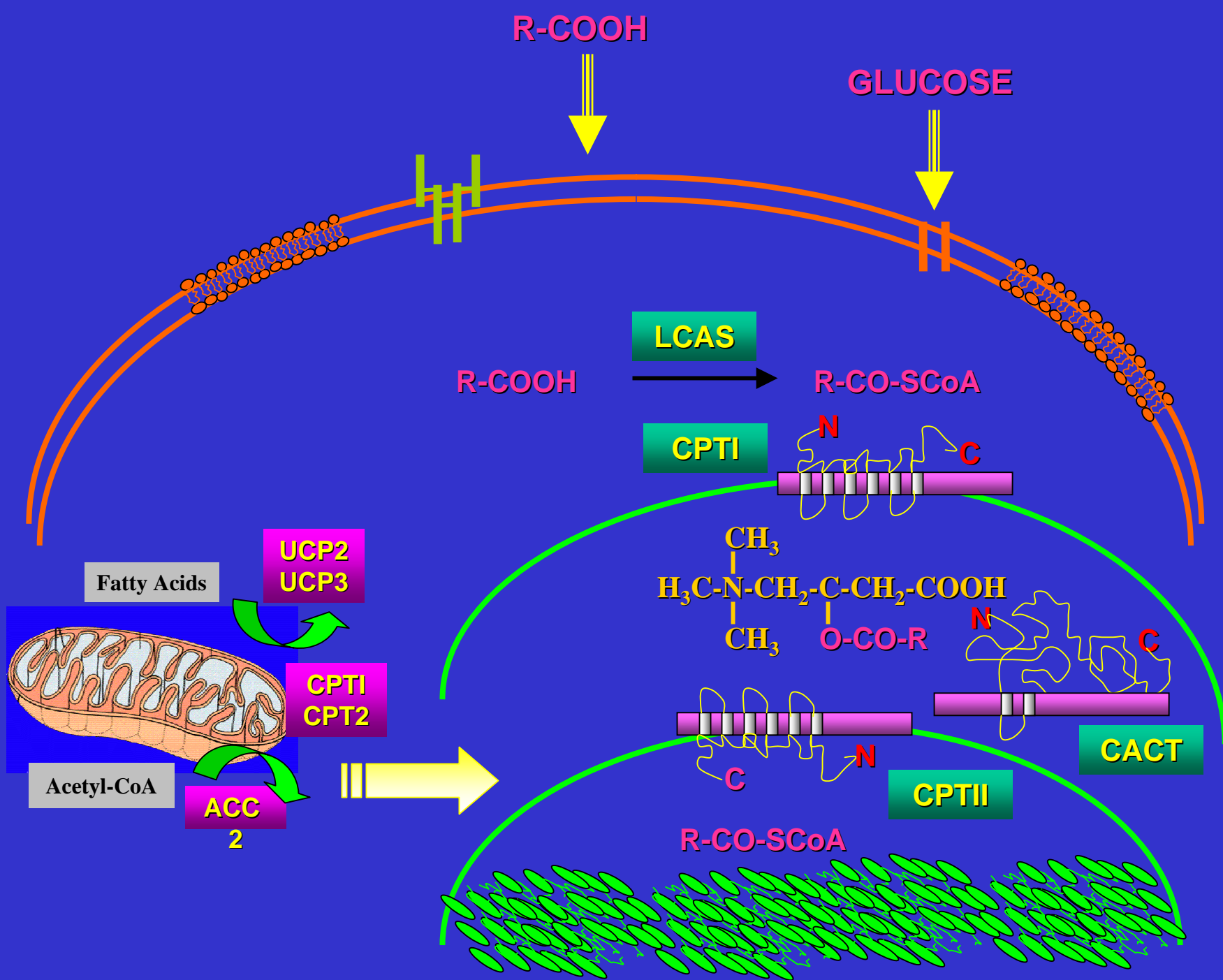
Wang H, EMBO J 1998



**The question is whether a mitochondrial dysfunction might be a co-factor in the development of type 2 DM**

**A 80% increase of the intramyocellular lipid content was observed in lean, insulin-resistant offspring of patients with type 2 diabetes compared with age and weight matched controls. These results support the hypothesis that insulin resistance is associated with a defect of muscle fatty acid oxidation.**

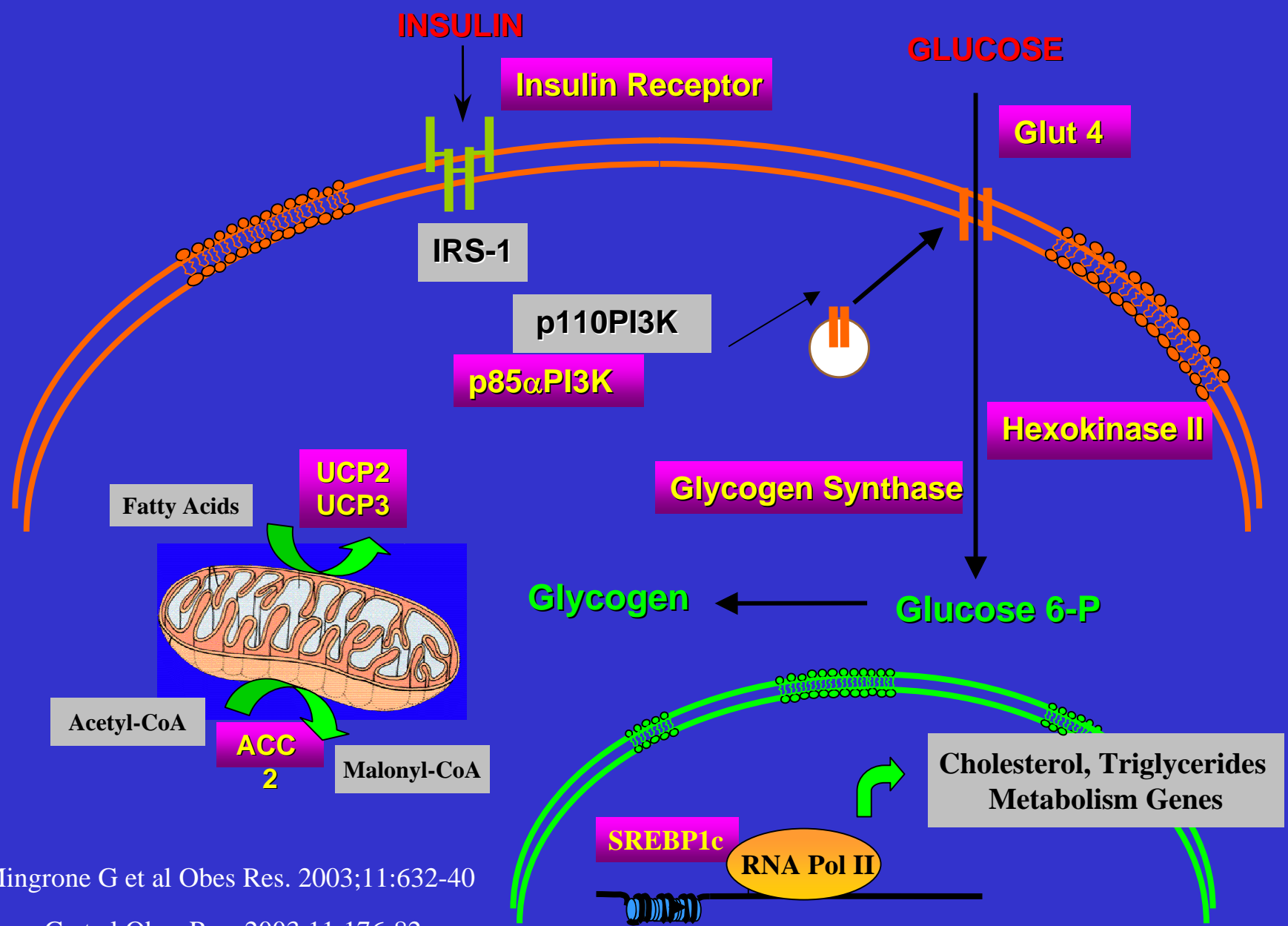
Petersen KF N Engl J Med 350:664-71; 2004



**Mitochondrial CACT concentration was decreased and carnitine-carnitine and acylcarnitine-carnitine exchange rates were significantly lower in IR subjects (n =19) than in controls (n = 11). The activity of other components of the mitochondrial carnitine system (i.e., carnitine palmitoyl transferase-I and II) was unchanged.**

**Our data suggest that by restraining entry of FA-coenzyme A into mitochondria, low CACT levels increase cytosolic FA levels and their incorporation into glycerolipids. The low level of CACT in IR muscle may contribute to the elevated muscle concentrations of triglycerides, diacylglycerol, and FA-coenzyme A characteristic of IR muscle.**





Mingrone G et al *Obes Res.* 2003;11:632-40

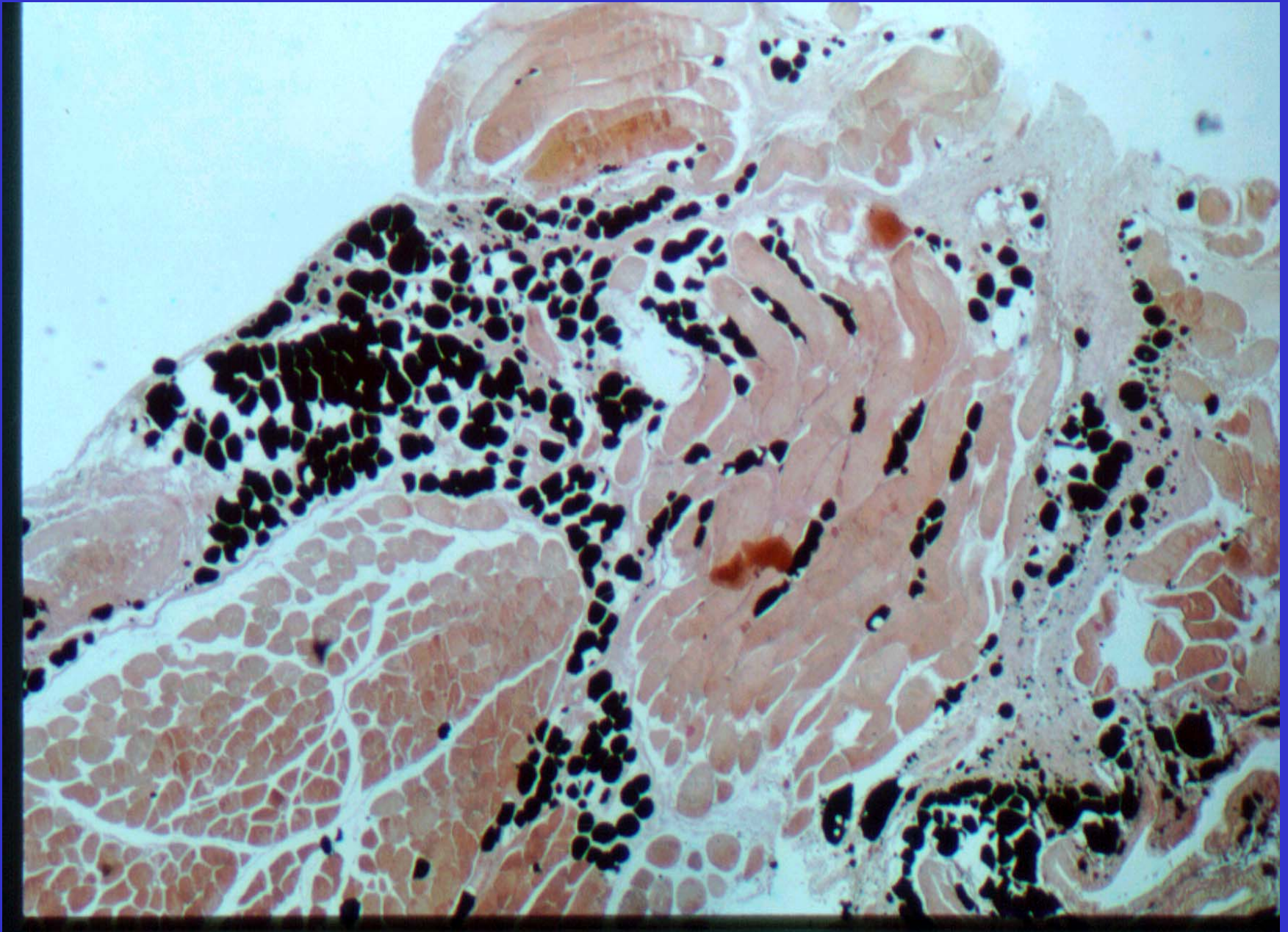
Rosa G et al *Obes Res.* 2003;11:176-82

Mingroner et al *Int J Obes Relat Metab Disord.* 2002;26:1165-72

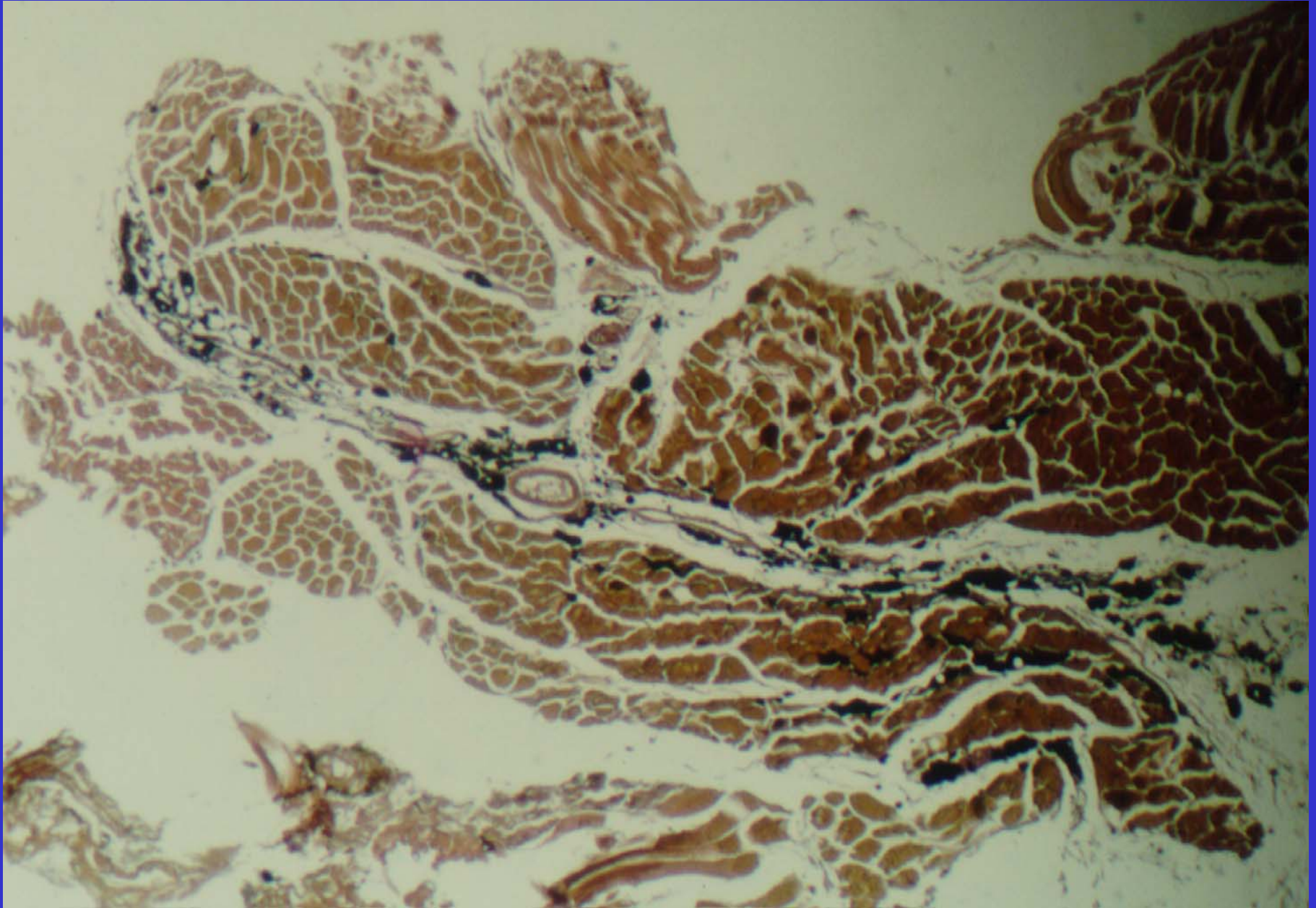
Greco et al *Diabetes.* 1999;48:1258-63

# PRE-BPD

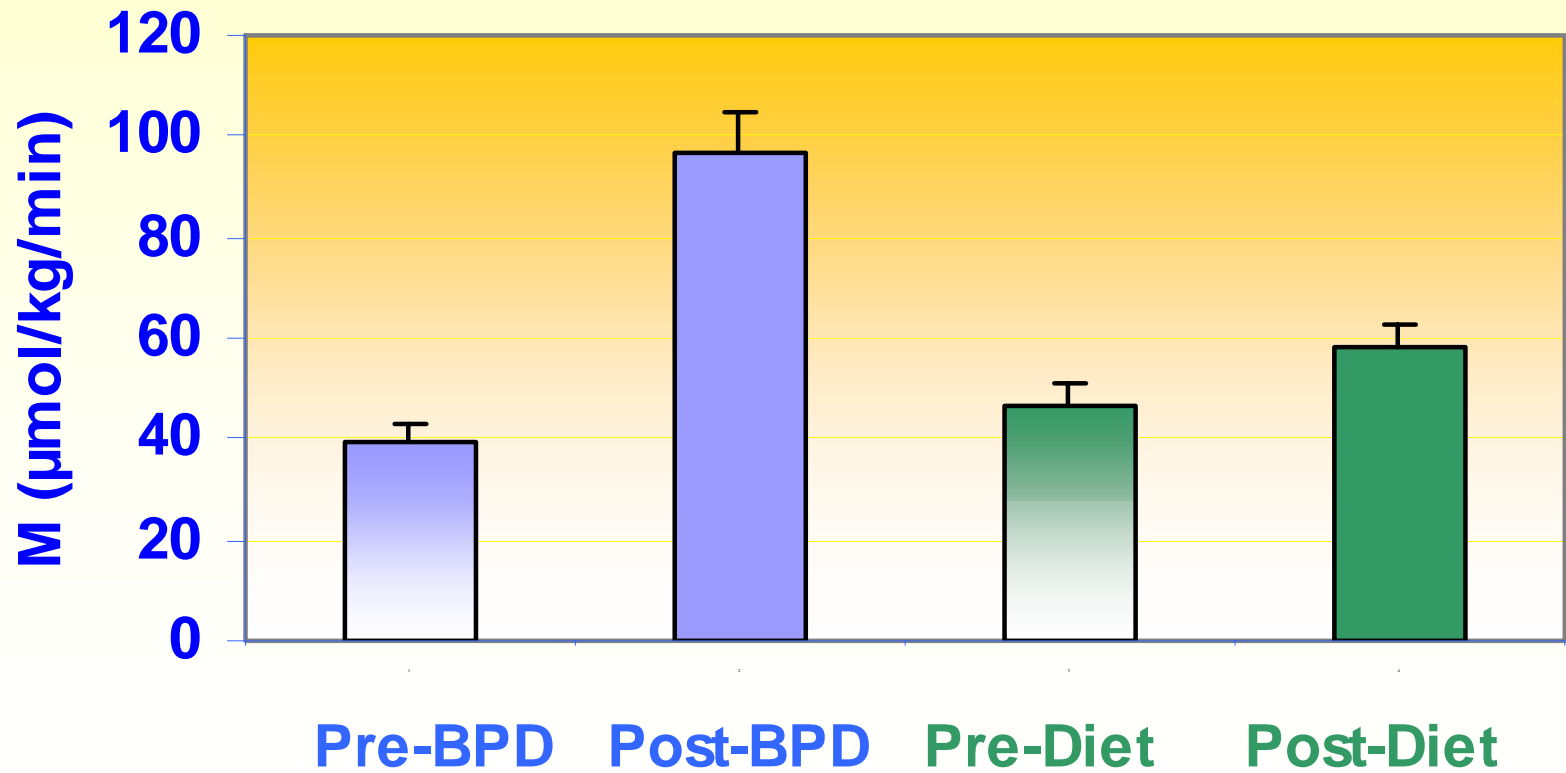
Greco et al.. Diabetes. 2002;51:144-51.



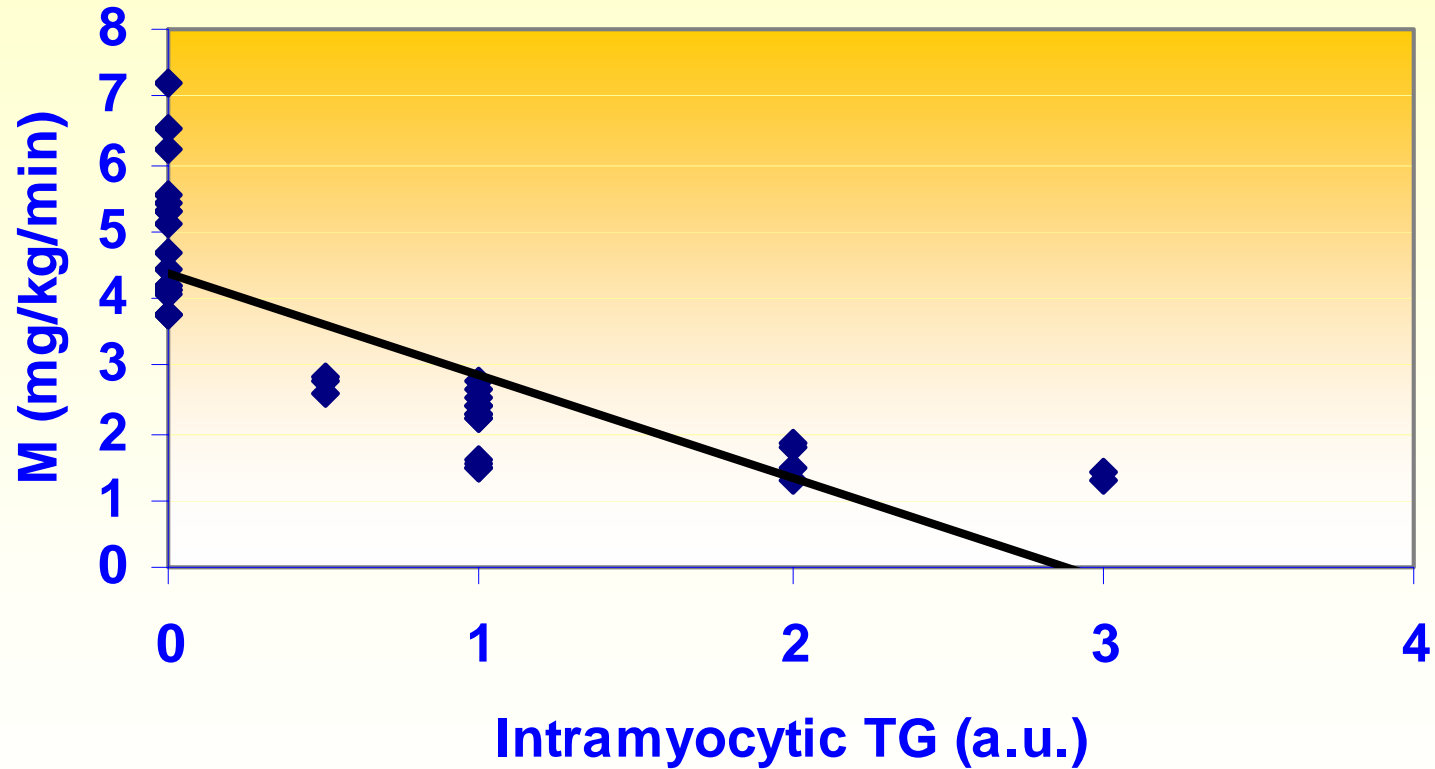
# POST-BPD

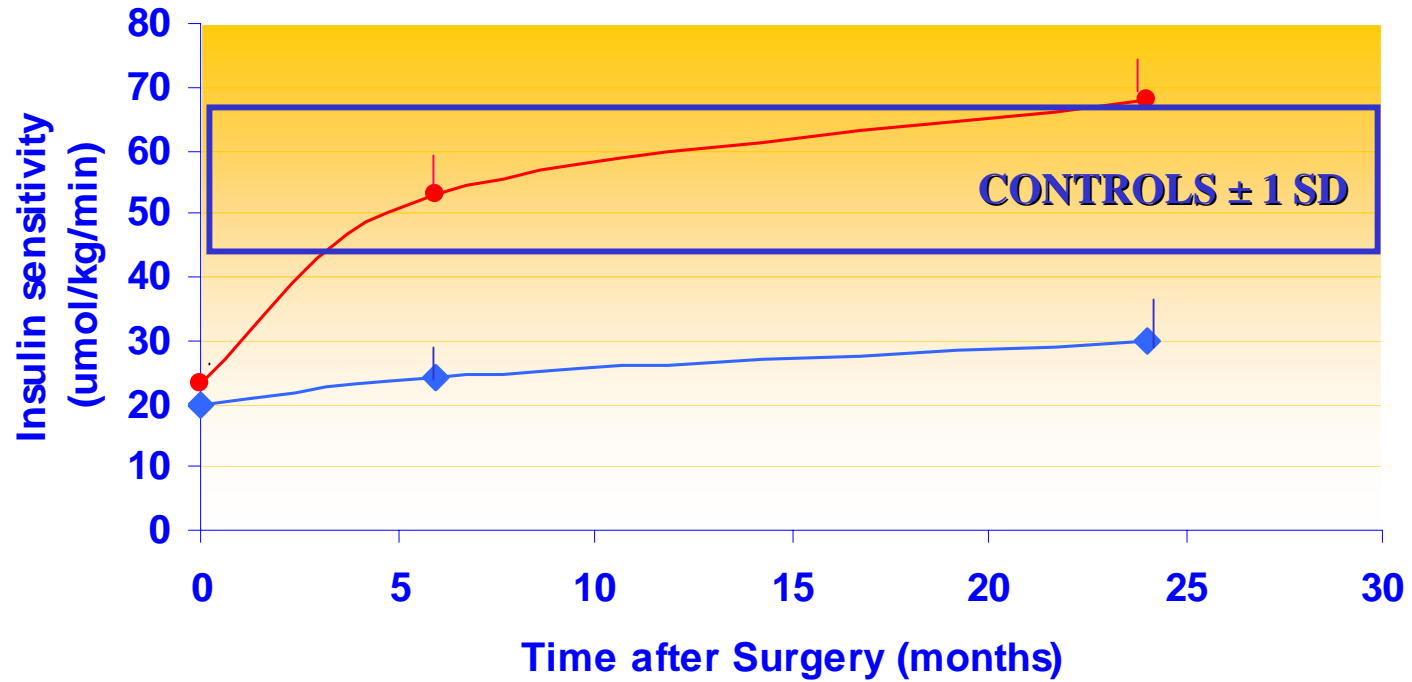


# EUGLYCEMIC HYPERINSULINEMIC CLAMP



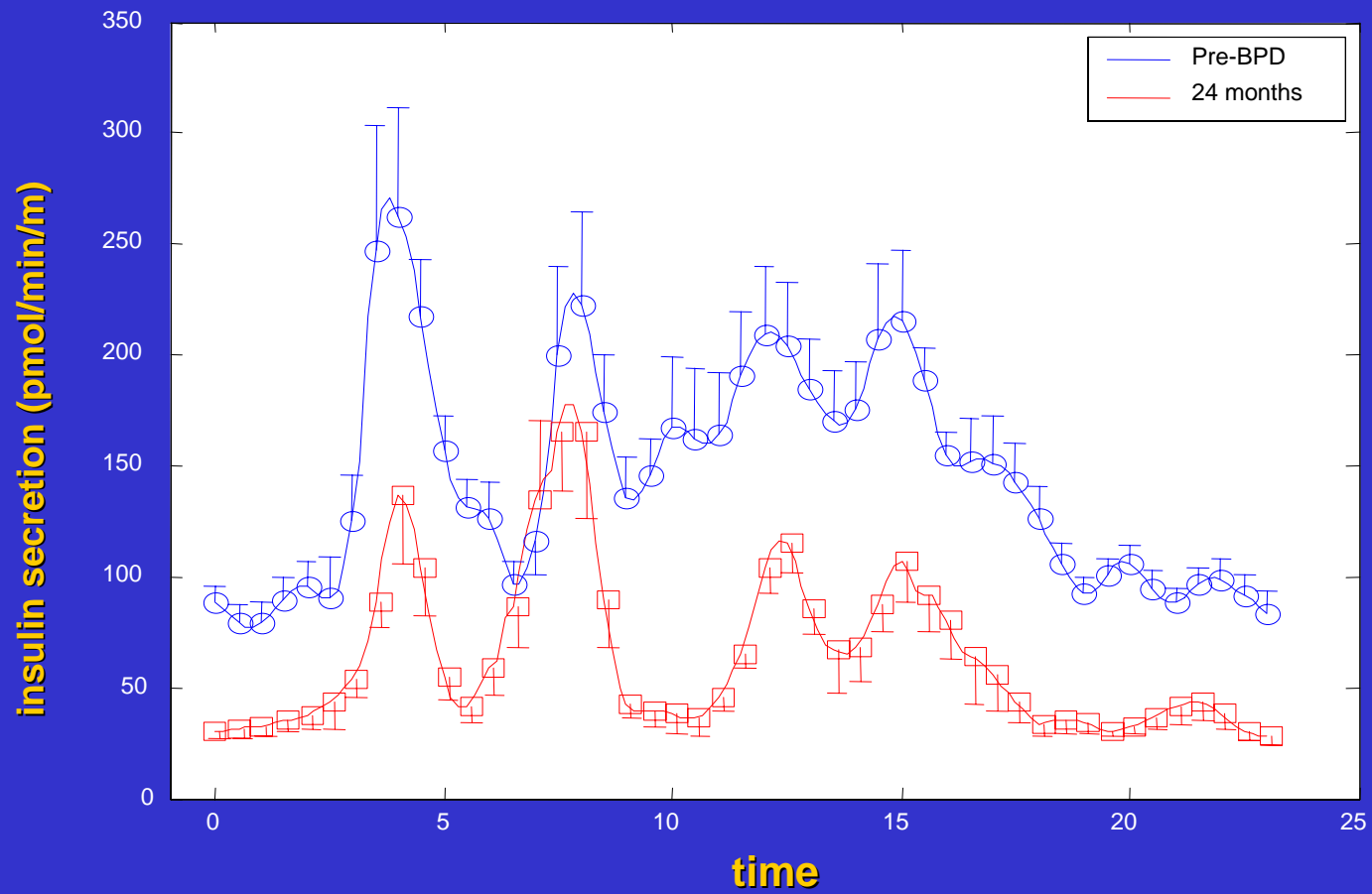
# LINEAR CORRELATION





**Blue diamonds = RY-GB**

**Red dots = BPD**



- Ferranni et al (Am J Physiol 1988) showed that L-carnitine increases non-oxidative glucose disposal by 50% in healthy volunteers.
- Capaldo et al. (Diab Res Clin Pract 1991) showed the same effect in type 2 diabetic patients.

## Minimal Modelling of Glucose Kinetics

- De Gaetano et al (Am Coll Nutr 1999) demonstrated a significant increase of both insulin sensitivity and glucose effectiveness in healthy volunteers after an i.v. bolus of L-carnitine.
- Mingrone et al (Am Coll Nutr 1999) showed in type 2 diabetic patients an increase of both glucose oxidation and non-oxidative glucose disposal.



# Anthropometric Characteristics

<b>Number of Subjects</b>	<b>18</b>
<b>Sex</b>	<b>8M/10F</b>
<b>Age (yrs)</b>	<b>52.3 ± 12</b>
<b>Weight (kg)</b>	<b>78.28 ± 15.8</b>
<b>Height (cm)</b>	<b>168 ± 12</b>
<b>BMI (kg* m<sup>-2</sup>)</b>	<b>27.46 ± 4.89</b>
<b>Fat Free Mass (kg)</b>	<b>57.63 ± 11.1</b>
<b>Fat Mass (kg)</b>	<b>20 ± 6.75</b>
<b>EE (kJ/24h) during saline infusion</b>	<b>6794.6 ± 1298</b>
<b>EE (kJ/24h) during ALC infusion</b>	<b>6810.8 ± 767</b>
<b>Fasting RQ during saline infusion</b>	<b>0.83 ± 0.04</b>
<b>Fasting RQ during ALC infusion</b>	<b>0.83 ± 0.02</b>

# Subjects


★ The studied sample consisted of 18 type 2 diabetic patients.


★ Patients were assigned randomly to the three active doses of Acetyl-L-Carnitine (ALC) by having 18 shuffled couples of drug vials marked by a progressive number and Day1/Day2 (double-blind with respect to both patient and physician conducting the experiment, both for dosage and for order active/placebo).

# Methods

- ★ **Body composition (DXA)**
- ★ **Indirect calorimetry**
- ★ **Euglycemic Hyperinsulinemic Clamp (EHC)**

# Research Design & Methods

 **Body composition was measured by DXA Fat-Free Mass (FFM) and Fat Mass (FM) were computed.**

 **Respiratory gas exchange was measured by an open-circuit ventilated-hood system and energy expenditure, respiratory quotient and substrate oxidation rate were calculated from O<sub>2</sub> consumption, CO<sub>2</sub> production, and N<sub>2</sub> urinary excretion.**

# Statistics 1

**Analysis of variance for repeated measures was performed on whole body glucose uptake (M) at end-clamp, end-clamp insulinemia (I), their ratio (M/I), end-clamp glucose storage (GST = M – End-clamp Glucose Oxidation), using sex (M, F) and administered dosage (0.025, 0.1, 1.0 mg/kg/min) as between-subject factors, ALC versus Placebo (ALC, P) as within-subjects factor, and anthropometric indices (BMI, Fat Mass, Fat-Free Mass, Age) as covariates.**

# Statistics 2

**A second type of repeated-measures design was employed to investigate the effect of ALC administration on the calorimetrically obtained metabolic descriptors (Energy Expenditure EE, Respiratory Quotient RQ, Glucose Oxidation GOX, Lipid Oxidation LOX). In this way the effect of ALC on producing differences in the change of these metabolic variables, under ALC infusion at baseline and under ALC infusion in the hyperinsulinemic state, was assessed.**

	Placebo	ALC 0.025	ALC 0.1	ALC 1.0
180 min		mg/kg <sub>bw</sub> /min	mg/kg <sub>bw</sub> /min	mg/kg <sub>bw</sub> /min
	(N=18)	(N = 6)	(N = 6)	(N = 6)

**M**  
(mg/kg<sub>bw</sub>/min)

3.81 ± 0.41	4.19 ± 0.84*	4.44 ± 0.56*	6.90 ± 1.34**
	(3.64 ± 0.60)	(3.98 ± 0.90)	(3.80 ± 0.74)

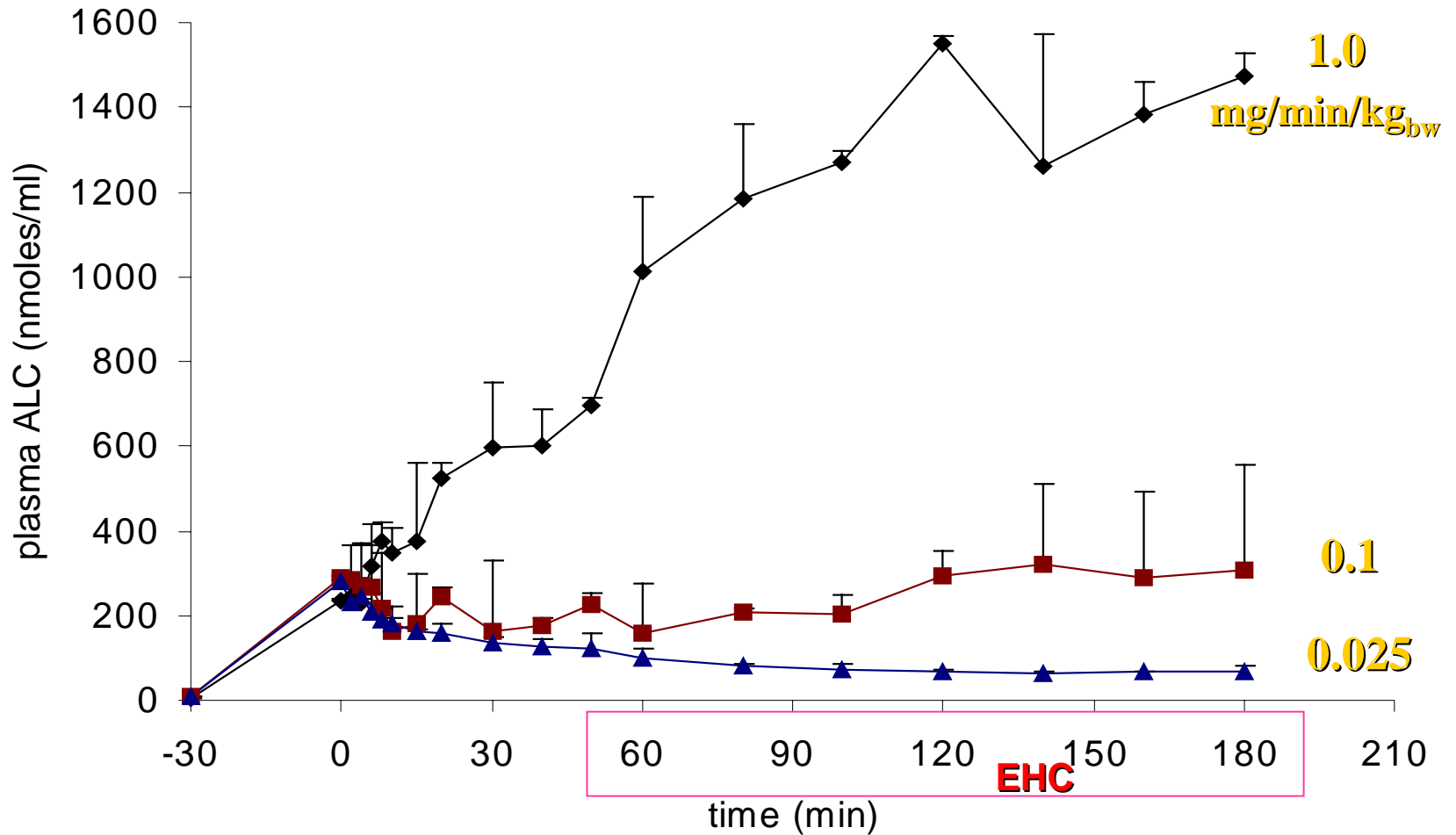
**M/I**  
(mg/kg<sub>bw</sub>/min)  
/ ( μUI/ml)

0.0382 ± 0.0054	0.0460 ± 0.013	0.0632 ± 0.011	0.0684 ± 0.011
	(0.0345 ± 0.012)	(0.0469 ± 0.011)	(0.0333 ± 0.004)

**Glucose storage**  
(mg/kg<sub>bw</sub>/min)

1.81 ± 0.36	2.47 ± 0.81*	2.08 ± 0.62*	4.61 ± 0.41**
	(1.87 ± 0.47)	(1.76 ± 0.86)	(1.79 ± 0.58)

# ALC Plasma Concentration





**The positive effect of ALC on glucose uptake occurred independently of the amount administered suggesting that it does not derive from the bulk delivery of acetyles to cells.**

**A possible explanation of this behavior would involve the modulation of gene expression (mitochondria? nucleus?), as proposed for liver and muscle cells in the mouse**

Giancaterini A, Metabolism, 2000

Hotta K Biochem Biophys Acta 1289: 131-135, 1996

Roncero C & Goodridge AG. Arch Biochem Biophys 295: 258-267, 1992



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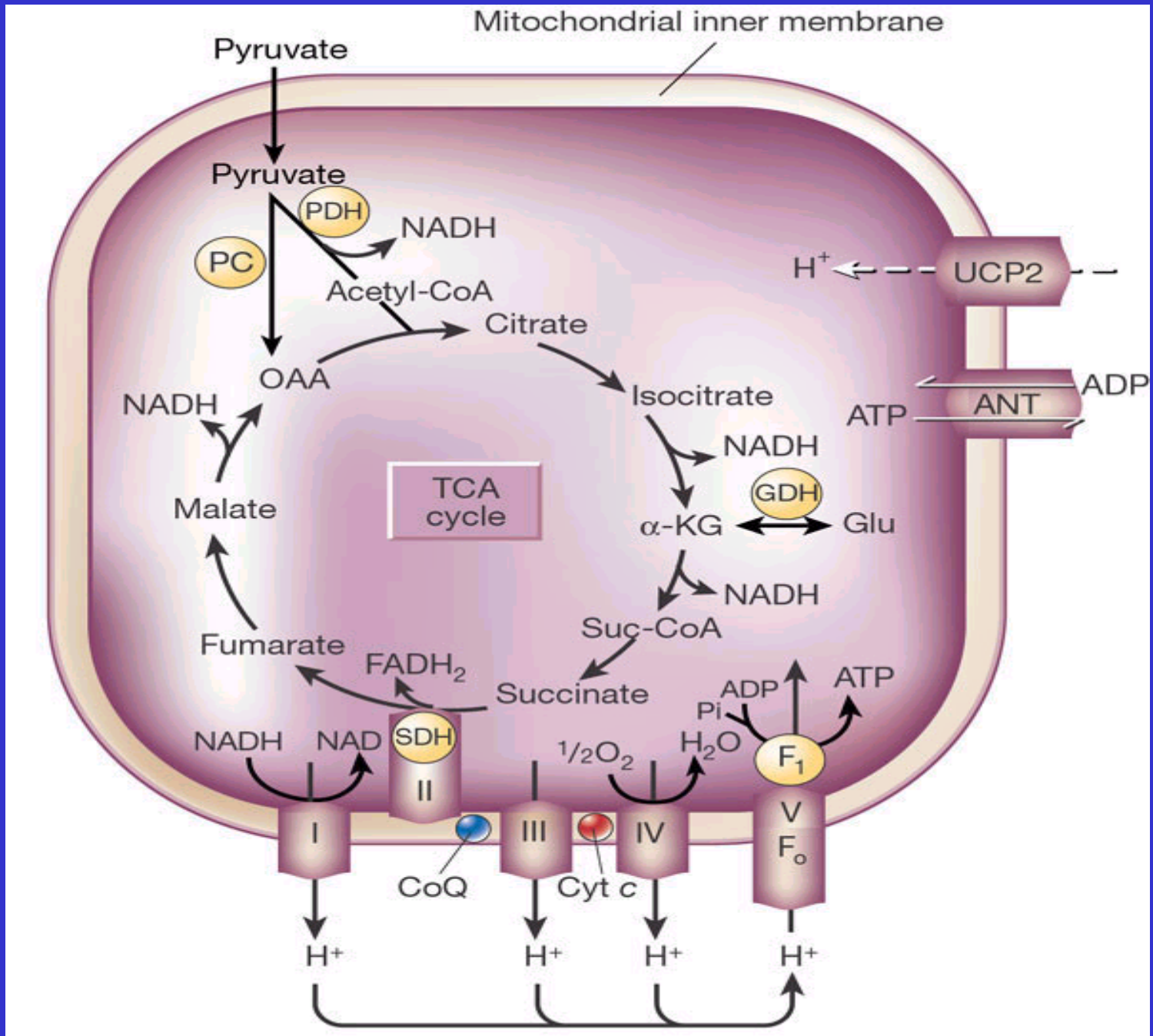
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**E. FERRANNINI  
A. GASTALDELLI  
S. CAMASTRA**



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**A. MARI**



# NEW PERSPECTIVES OF RESEARCH

Clinical data support the hypothesis that insulin resistance in the

skeletal muscle of insulin-resistant offspring of patients with type 2

diabetes is associated with dysregulation of intramyocellular fatty

(Petersen KF, N Engl J Med 350:664-671; 2004)

acid metabolism, possibly because of an inherited defect in mitochondrial oxidative phosphorylation

It is noteworthy to verify whether or not L-carnitine may contribute to improve fatty acid oxidation or oxidative phosphorylation.

**Do L-carnitine and/or its esters modulate lipid metabolism gene expression? PPAR $\alpha$  PPAR $\gamma$ , etc.**

# CONCLUSIONS

**The positive effect of ALC on glucose uptake occurred independently of the amount administered suggesting that it does not derive from the bulk delivery of acetyles to cells.**

**A possible explanation of this behavior would involve the modulation of gene expression, as proposed for liver and muscle cells in the mouse and chick embryo hepatocytes.**

Hotta K Biochem Biophys Acta 1289: 131-135, 1996

Roncero C & Goodridge AG. Arch Biochem Biophys 295: 258-267, 1992