Obesity and Type 2 Diabetes In Children

A Biochemical Viewpoint

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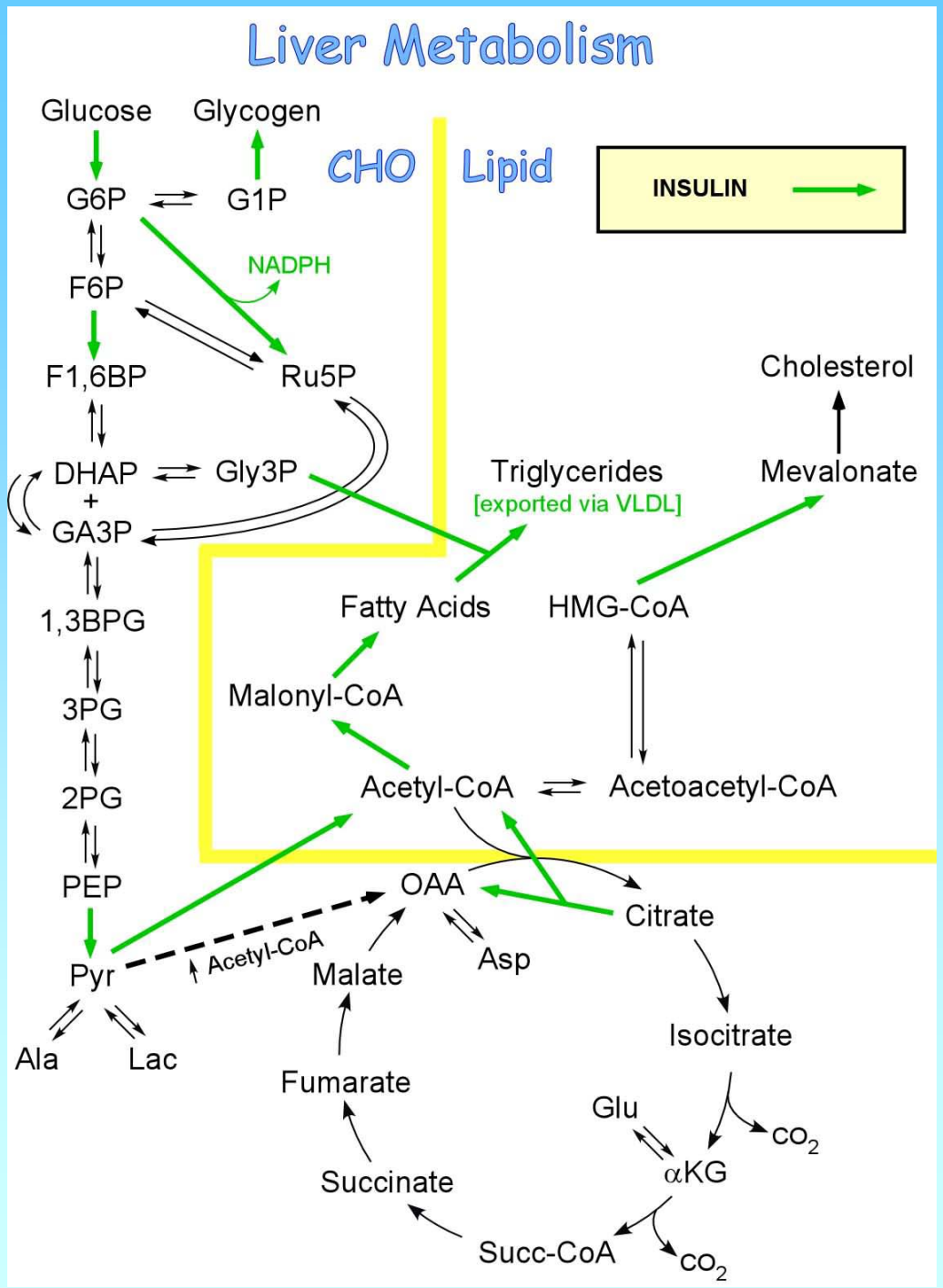
Why are American Children Getting Fatter?

- U.S. diets are lower in fat content but higher in carbohydrate
- Insulin stimulates anabolic processes
- Carbohydrate is efficiently converted to triglycerides in the liver

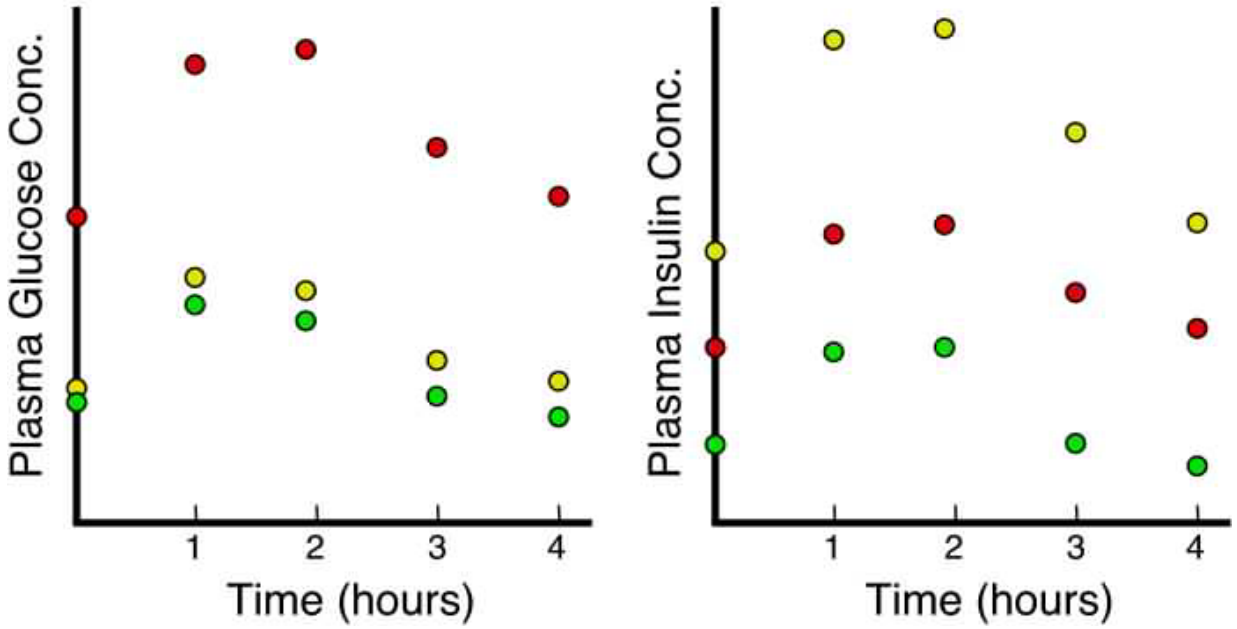
Too many calories –
Not enough exercise


Liver Metabolism
Glucose
Glycogen
CHO
Lipid
INSULIN
G6P
G1P
NADPH
F6P
F1,6BP
Ru5P
Cholesterol
DHAP
Gly3P
+
GA3P
Triglycerides
[exported via VLDL]
Mevalonate
1,3BPG
Fatty Acids
HMG-CoA
Malonyl-CoA
3PG
2PG
Acetyl-CoA
Acetoacetyl-CoA
PEP
OAA
Citrate
Pyr
Acetyl-CoA
Malate
Asp
Isocitrate
Ala
Lac
Fumarate
Glu
CO_2
αKG
Succinate
Succ-CoA
CO_2

Normal Weight Non-Diabetic

Obese Non-Diabetic

Obese Diabetic



Obesity → **Hyperinsulinemia**

Hyperinsulinemia → **Diabetes**

Many Obese Youth Have Condition That Precedes Type 2 Diabetes
Studies To Address Obesity-Linked Diabetes in Children

Many obese children and adolescents have impaired glucose tolerance, a condition that often appears before the development of type 2 diabetes, according to researchers funded by the National Institutes of Health (NIH). The study findings appear in the March 14, 2002 issue of *The New England Journal of Medicine*.

"This study suggests that many obese children have a high risk for developing type 2 diabetes," said HHS Secretary Tommy G. Thompson. "Researchers have a lot of information on how to prevent and treat type 2 diabetes in adults, but we need to find better ways to prevent and treat the disease in children.“

Once seen only in adults, type 2 diabetes has been rising steadily in children, especially minority adolescents-African Americans, Hispanic Americans, and Native Americans, according to reports from clinics around the country. Although there are no national, population-based data, studies in Cincinatti, Charleston, Los Angeles, San Antonio, and other cities indicate that the percentage of children with newly diagnosed diabetes who are classified as having type 2 diabetes has risen from less than 5 percent before 1994 to 30-50 percent in subsequent years.

"These results strongly imply that intensive efforts to reduce obesity in children and youth who have impaired glucose tolerance will help to prevent their developing type 2 diabetes," said Duane Alexander, M.D., Director of the National Institute of Child Health and Human Development (NICHD). Both NICHD and the National Center for Research Resources (NCRR), another NIH component, funded the study. Both agencies are part of the National Institutes of Health, the HHS agency that sponsors research to uncover knowledge that will lead to better health for everyone.

The scientists from Yale University School of Medicine conducted their study to determine if obese children and teens have impaired glucose tolerance, which, in adults is a known risk factor for type 2 diabetes. The researchers found that the children with impaired glucose tolerance frequently had insulin resistance, a condition that usually precedes type 2 diabetes in adults and is characterized by the inability of fat, muscle, and liver cells to use insulin properly. Eventually, the insulin-producing cells of the pancreas cannot keep up with the body's increasing demand for insulin, glucose builds up in the blood, and type 2 diabetes begins.

"The epidemic of childhood obesity in the United States has been accompanied by a marked increase in the frequency of type 2 diabetes," the study authors wrote.

The researchers tested for impaired glucose tolerance in 55 obese children from 4 to 10 years of age, and 112 obese adolescents from 11 to 18 years of age. In all, 25 percent of the children and 21 percent of the adolescents had impaired glucose tolerance. The researchers also found that four of the adolescents in the study had silent type 2 diabetes, a form of diabetes that doesn't cause any symptoms.

"Impaired glucose tolerance is highly prevalent among children and adolescents with severe obesity, irrespective of ethnic group," the researchers wrote.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the part of the NIH with lead responsibility for diabetes research, is funding clinical trials to prevent and treat type 2 diabetes in children. These studies, currently being planned for recruitment in 2003, will try to develop ways to stem the rising rate of type 2 diabetes in children and to treat the disease safely and effectively in those who do develop it.

The prevention trials will focus on developing cost-effective interventions that can be widely applied in schools and communities across the country. "For children who already have type 2 diabetes, it's critical to give the safest, most effective therapy as early as possible, yet we can't assume that the therapies used in adults have the same safety and efficacy profiles for children," said study chair Dr. Francine Kaufman, president elect of the American Diabetes Association and director of the Comprehensive Diabetes Center at the Children's Hospital of Los Angeles. Many drugs are available to treat type 2 diabetes, but only metformin has been explicitly approved by the Food and Drug Administration for the treatment of type 2 diabetes in children.

The longer a person has diabetes, the greater the chances of developing the disabling, life-threatening complications of diabetes. "We are seeing young people in their late teens who are already developing the complications of type 2 diabetes," said Dr. Kaufman.

Type 2 diabetes in children, as in adults, is closely linked to obesity, a sedentary lifestyle, and a family history of diabetes. The prevalence of obesity has nearly tripled in adolescents in the past 20 years.

According to *The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity*, 13 percent of children 6 to 11 years old and 14 percent of adolescents 12 to 19 years old in the United States were overweight in 1999.

Overweight children are at increased risk of developing type 2 diabetes during childhood and later in life. Genetic susceptibility as well as lack of physical activity and unhealthy eating patterns all play important roles in determining a child's weight. They also contribute to a child's risk for type 2 diabetes and other complications of overweight.

Prevention and Treatment of Obesity

- Diet
- Lifestyle
- Pharmaceutical intervention

Xenical (orlistat)

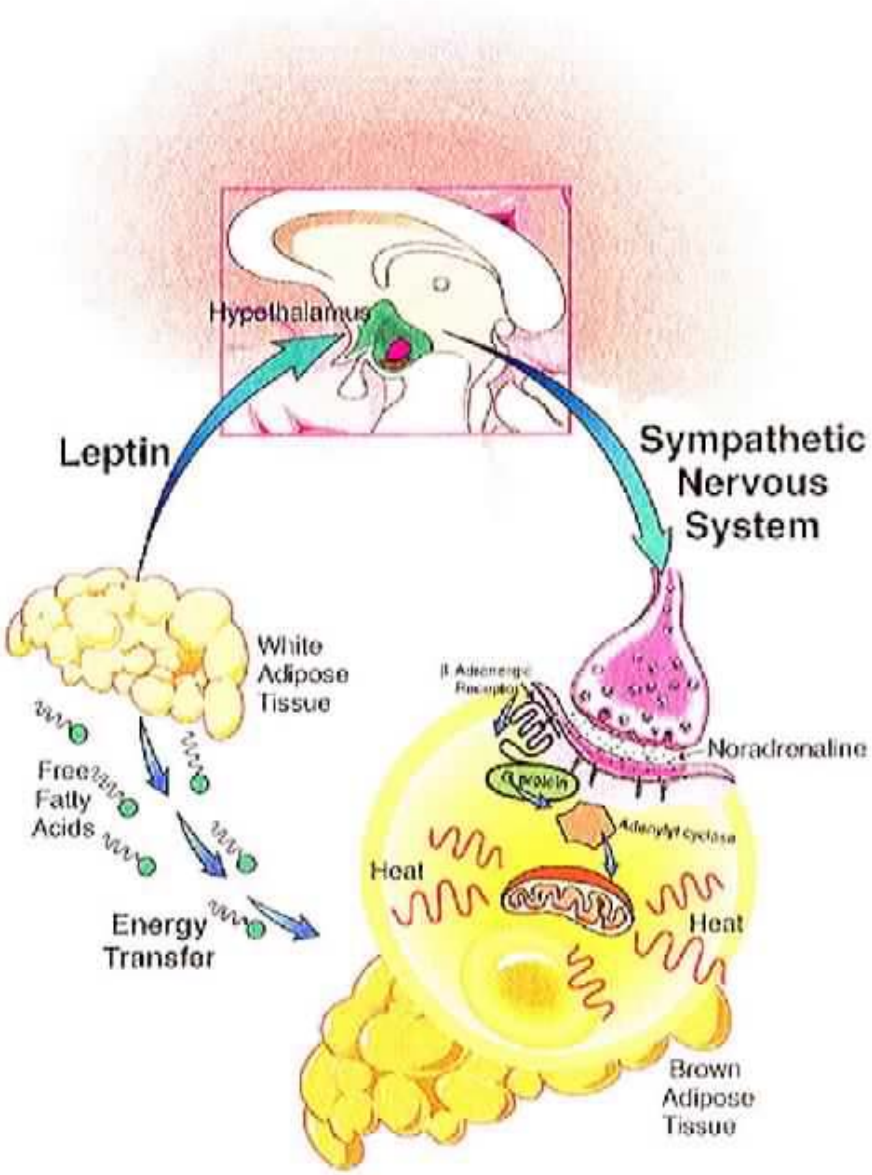
- Developed by Hoffmann-La Roche
- Approved in 1999 by FDA for obese patients with BMI > 30
- Inhibits activity of pancreatic lipase
- Decreases fat-soluble vitamin and carotenoid absorption

Olean (olestra)

- Developed by Procter & Gamble
- Approved in 1995 by FDA for use in snack foods
- BUT interferes with fat-soluble vitamin absorption
- May decrease blood levels of carotenoids (increasing heart disease & cancer)

Leptin

- Discovered by Friedman in 1994
- Product of ob gene in mice
- Also found in humans
- Synthesized in fat cells
- Signals brain to decrease food intake and increase metabolism
- Potential treatment for obesity?


Hypothalamus
Leptin
Sympathetic Nervous System
White Adipose Tissue
Free Fatty Acids
Energy Transfer
Noradrenaline
Heat
Heat
Brown Adipose Tissue

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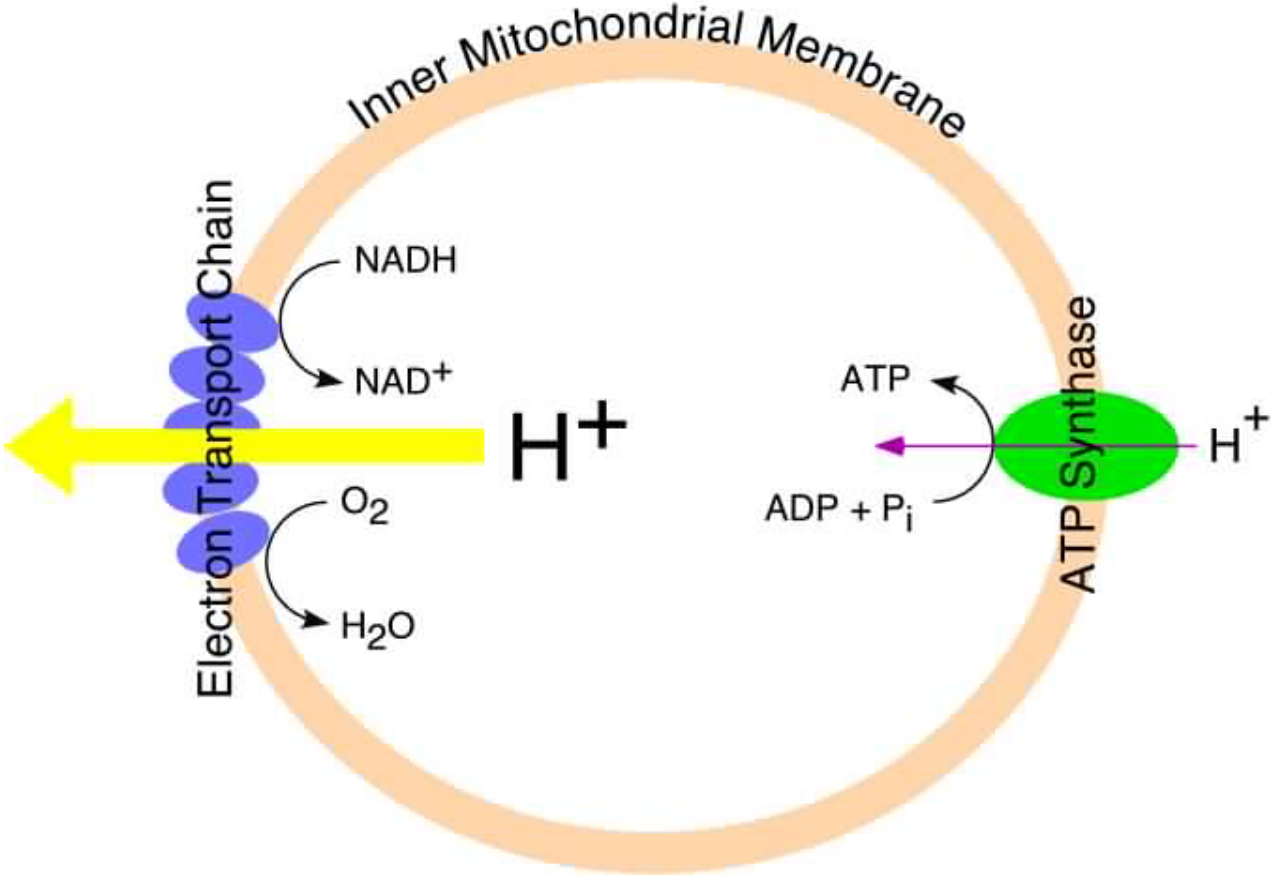
Mice overexpressing human uncoupling protein-3 in skeletal muscle are hyperphagic and lean

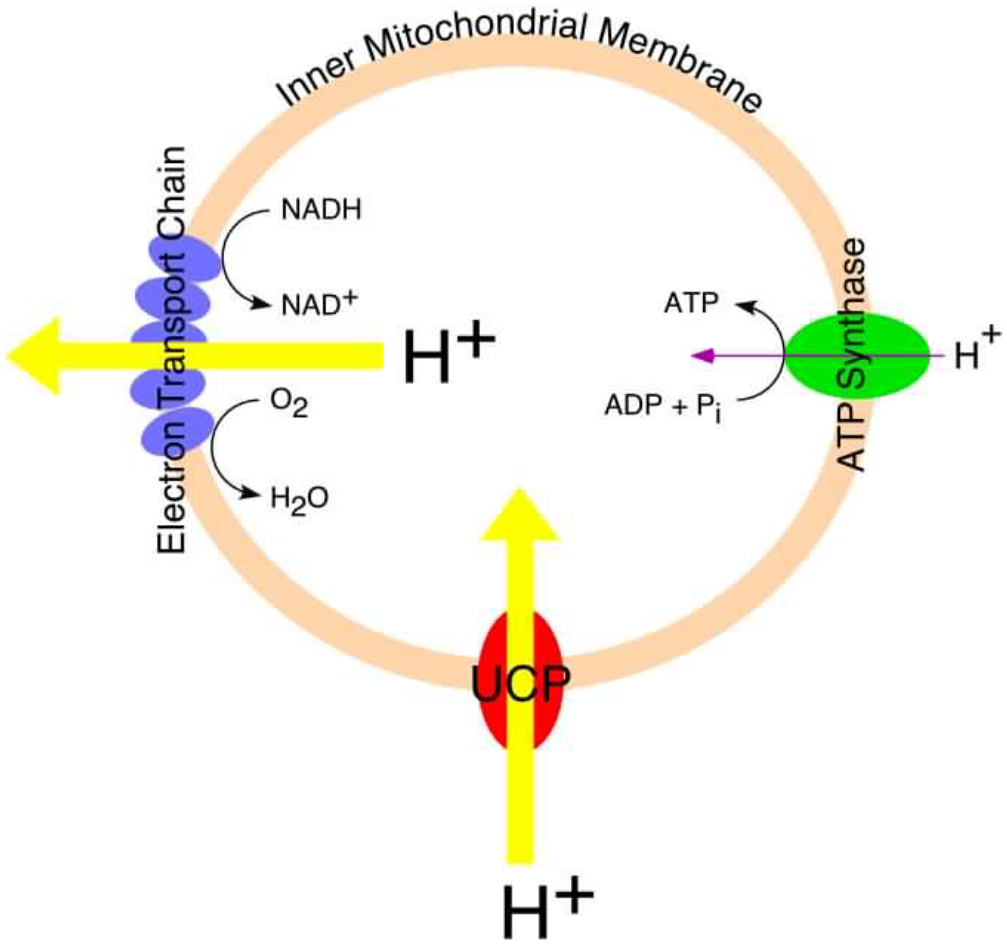
John C. Clapham*, Jonathan R. S. Arch*, Helen Chapman*, Andrea Haynes*, Carolyn Lister*, Gary B. T. Moore*, Valerie Piercy*, Sabrina A. Carter*, Ines Lehner*, Stephen A. Smith*, Lee J. Beeley••, Robert J. Godden§, Nicole Herrityk, Mark Skehel¶, K. Kumar Changani#, Paul D. Hockings#, David G. Reid#, Sarah M. Squires#, Jonathan Hatcher

Uncoupling protein–3 (UCP-3) is a recently identified member of the mitochondrial transporter superfamily that is expressed predominantly in skeletal muscle. However, its close relative UCP-1 is expressed exclusively in brown adipose tissue, a tissue whose main function is fat combustion and thermogenesis. Studies on the expression of UCP-3 in animals and humans in different physiological situations support a role for UCP-3 in energy balance and lipid metabolism. However, direct evidence for these roles is lacking. Here we describe the creation of transgenic mice that overexpress human UCP-3 in skeletal muscle. These mice are hyperphagic but weigh less than their wild-type littermates. Magnetic resonance imaging shows a striking reduction in adipose tissue mass. The mice also exhibit lower fasting plasma glucose and insulin levels and an increased glucose clearance rate. This provides evidence that skeletal muscle UCP-3 has the potential to in¯uence metabolic rate and glucose homeostasis in the whole animal.

Oxidative Phosphorylation

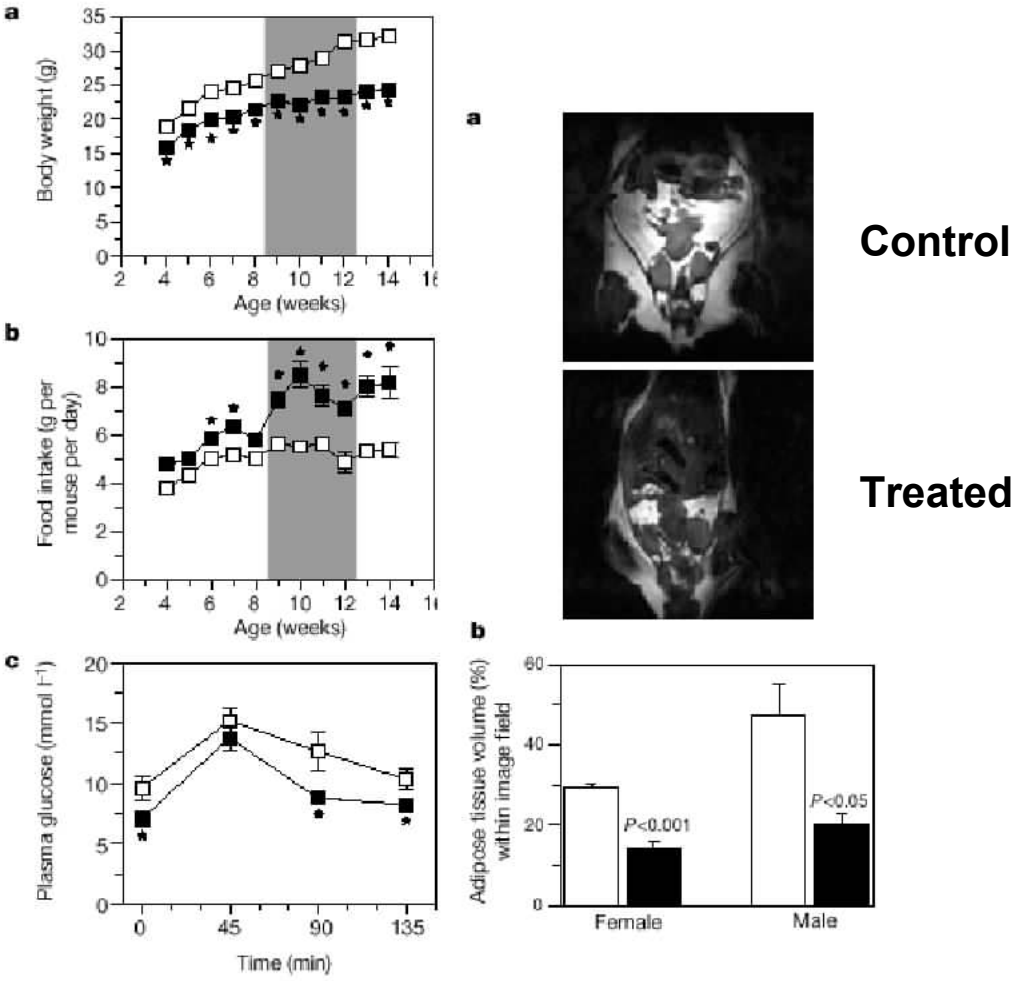


Uncoupling Protein



White = Control Mice

Black = Treated Mice



Control

Treated

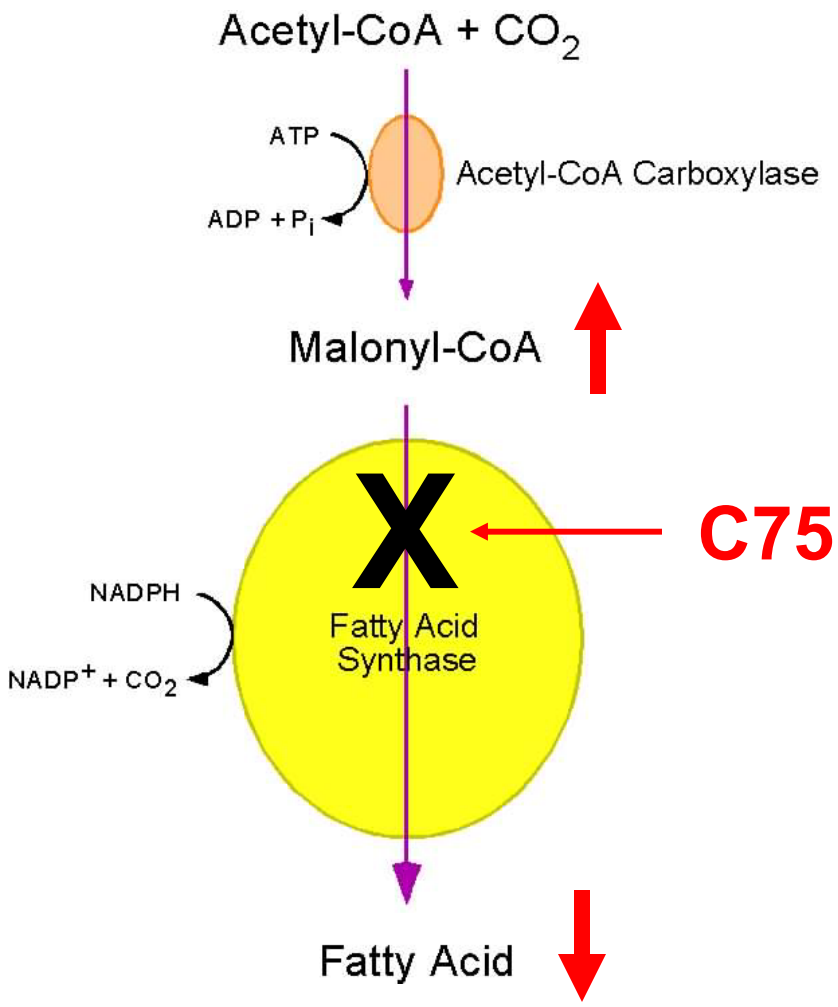
Science 288 (2000) 2379-2381

Reduced Food Intake and Body Weight in Mice Treated with Fatty Acid Synthase Inhibitors

Thomas M. Loftus, Donna E. Jaworsky, Gojeb L. Frehywot,
Craig A. Townsend, Gabriele V. Ronnett, M. Daniel Lane,
Francis P. Kuhajda *

With the escalation of obesity-related disease, there is great interest in defining the mechanisms that control appetite and body weight. We have identified a link between anabolic energy metabolism and appetite control. Both systemic and intracerebroventricular treatment of mice with fatty acid synthase (FAS) inhibitors (cerulenin and a synthetic compound C75) led to inhibition of feeding and dramatic weight loss. C75 inhibited expression of the prophagic signal neuropeptide Y in the hypothalamus and acted in a leptin-independent manner that appears to be mediated by **malonyl-coenzyme A**. Thus, FAS may represent an important link in feeding regulation and may be a potential therapeutic target.

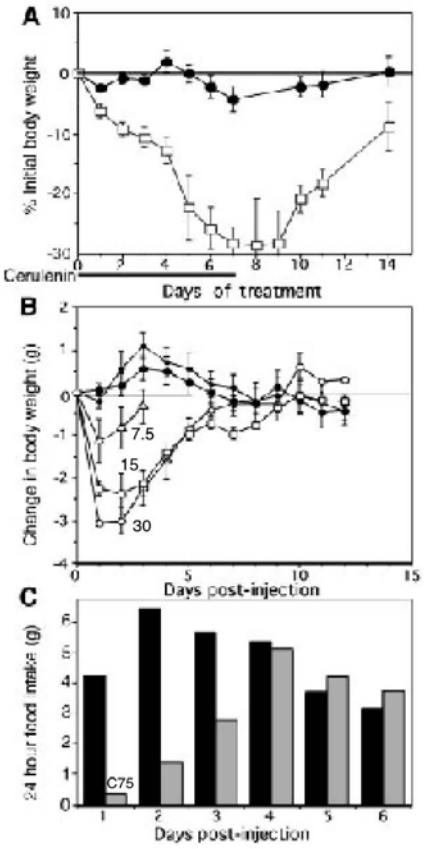
Inhibition of FAS



Inhibition of FAS

Effect of C75 on

Leptin-deficient mice

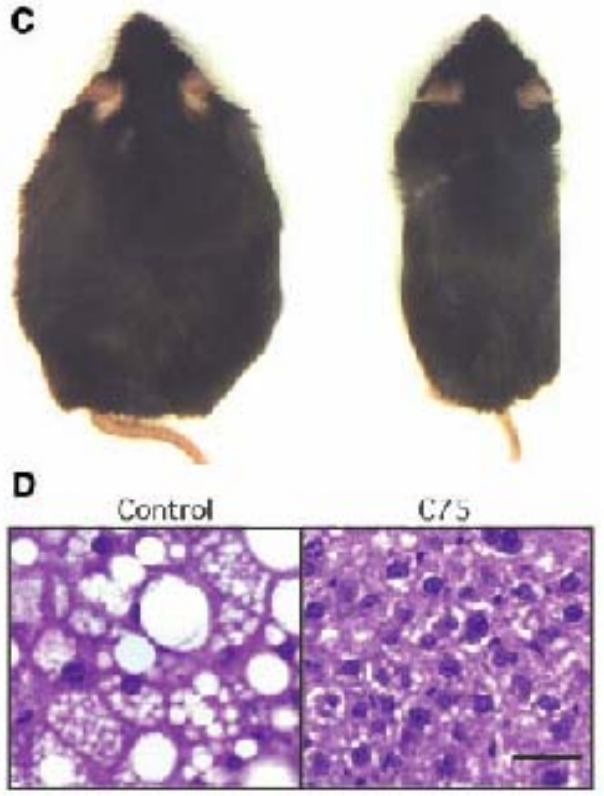


Inhibition of FAS

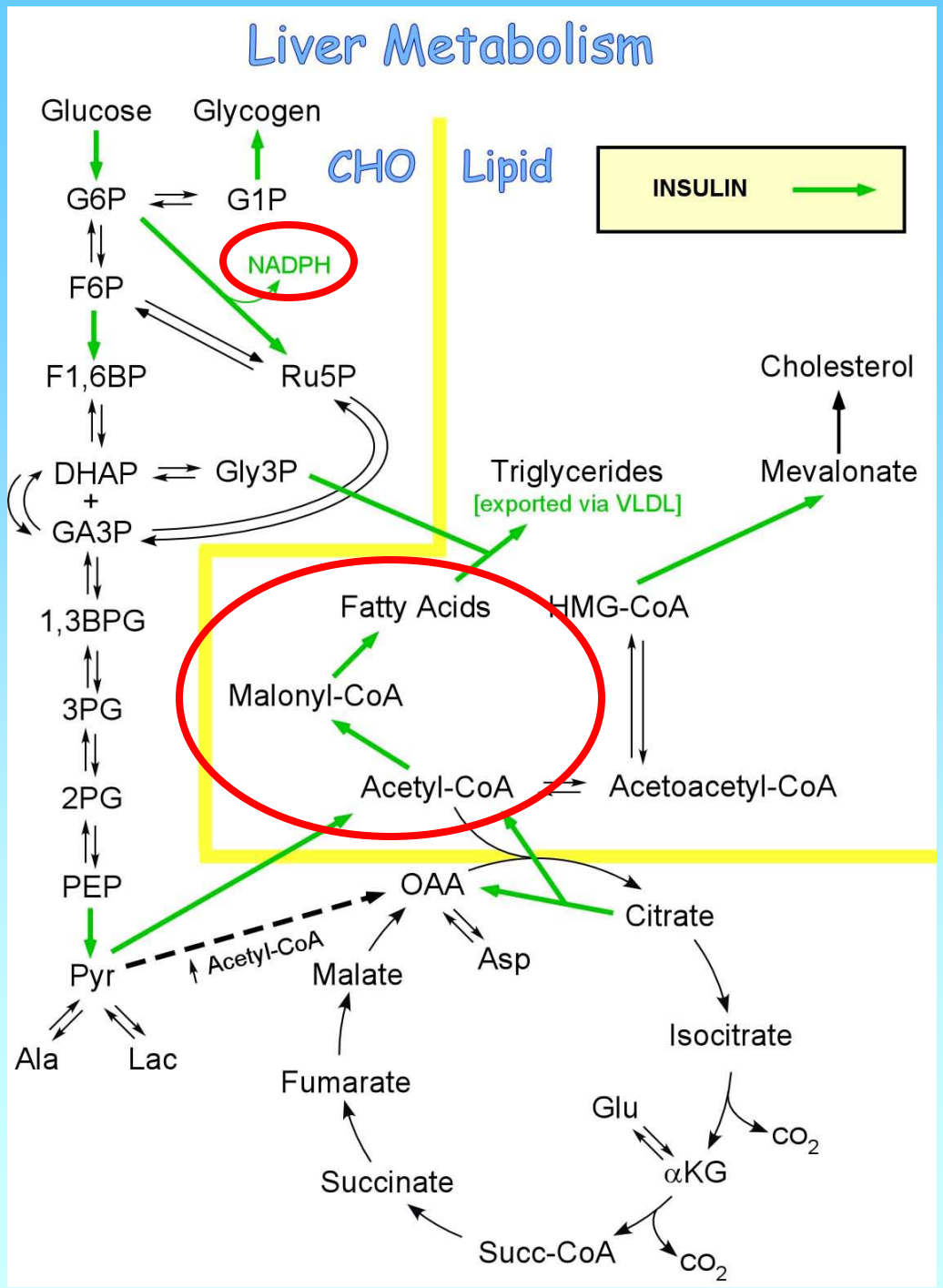
Effect of C75 on

Leptin-deficient mice

After 14 days of treatment



Tissue sections of liver


Liver Metabolism
Glucose
Glycogen
CHO
Lipid
INSULIN
G6P
G1P
NADPH
F6P
F1,6BP
Ru5P
Cholesterol
DHAP
Gly3P
+
GA3P
Triglycerides
[exported via VLDL]
Mevalonate
1,3BPG
Fatty Acids
HMG-CoA
Malonyl-CoA
3PG
2PG
Acetyl-CoA
Acetoacetyl-CoA
PEP
OAA
Citrate
Pyr
Acetyl-CoA
Malate
Asp
Isocitrate
Ala
Lac
Fumarate
Glu
CO_2
Succinate
αKG
Succ-CoA
CO_2

NIH Obesity Research Task Force

The complexity and urgency of the problem of obesity require that the NIH take a more collaborative and multi-disciplinary approach to obesity research. Thus, the NIH Director, in the Spring of 2003, created the NIH Obesity Research Task Force as a new effort to facilitate progress in obesity research across the NIH. Co-chaired by the Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by the Acting Director of the National Heart, Lung, and Blood Institute (NHLBI), the membership of the NIH Obesity Research Task Force consists of representatives from these and numerous other NIH ICs. As part of its charge from the NIH Director, the Task Force is currently in the process of developing a Strategic Plan for obesity research that will include short- and long-term goals encompassing basic and clinical research.

Strategic Planning Process

--Preventing and treating obesity through behavioral and environmental approaches to modify lifestyle.

--Preventing and treating obesity through pharmacologic, surgical, or other biological/medical approaches.

--Breaking the link between obesity and its associated health conditions, such as type 2 diabetes, heart disease, cancer, and numerous other health problems.

--Cross-cutting research topics, including, for example, research resources, multidisciplinary research teams, investigator training, translational research (progressing from basic science to clinical studies and from clinical-trial results to community interventions), and dissemination of research results to the public.

An important focus of efforts in these areas will be health issues in specific populations, such as, for example, children and racial/ethnic minorities.