Obesity and Type 2 Diabetes In Children

A Biochemical Viewpoint

Jack Blazyk, Ph.D.

Professor of Biochemistry

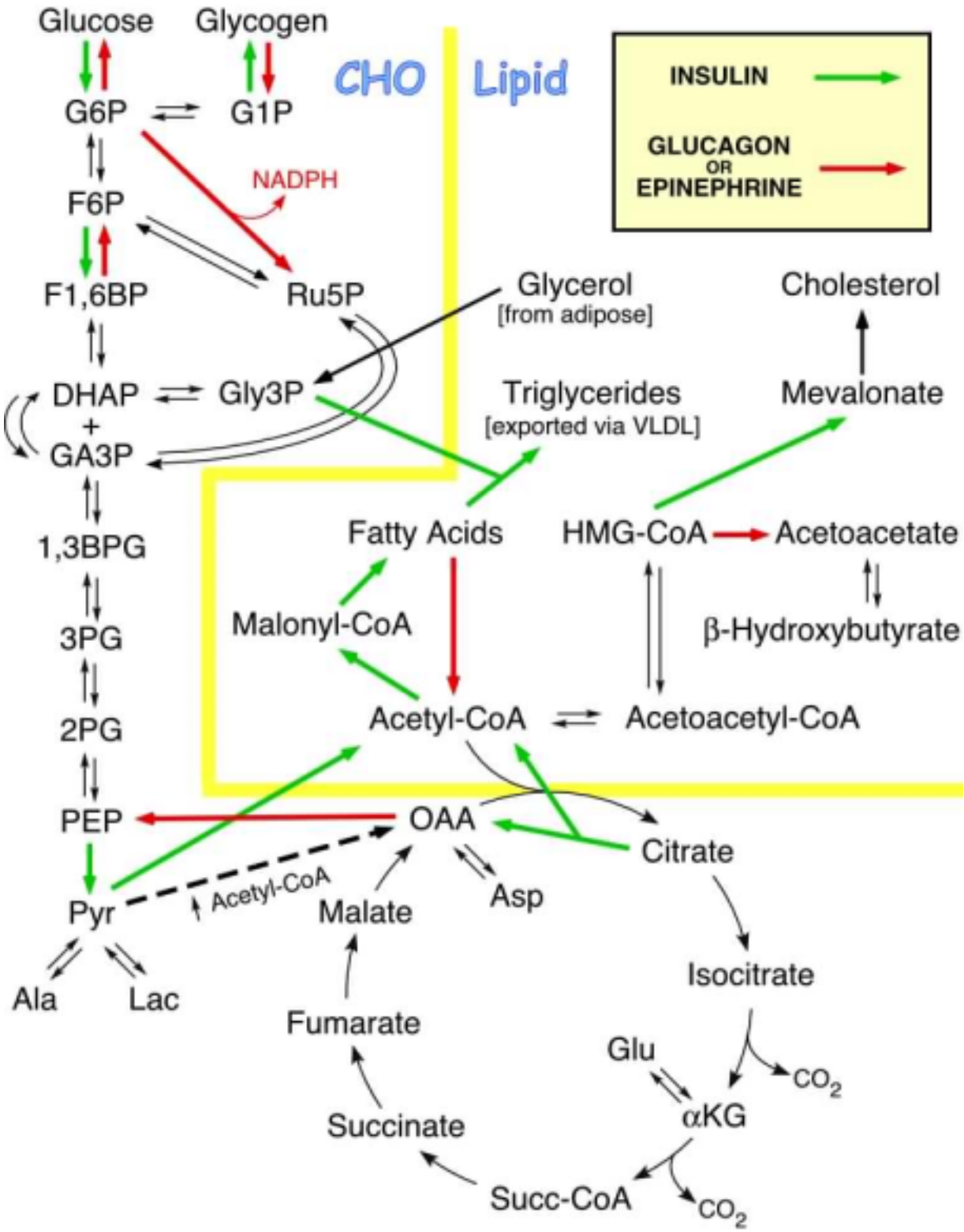
Department of Biomedical Sciences

Ohio University College of Osteopathic Medicine

- Obesity in children has increased dramatically
- 1 out of 4 children in the U.S. is obese
- The rise in obesity parallels a rise in type 2 diabetes

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

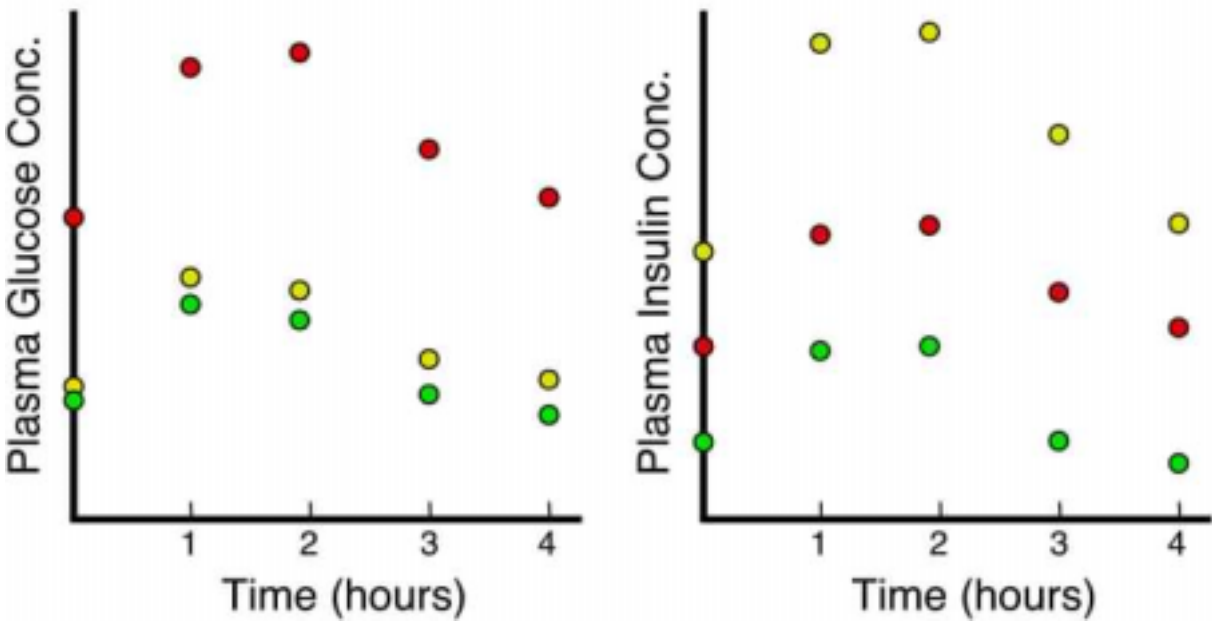
Liver Metabolism



Normal Weight Non-Diabetic

Obese Non-Diabetic

Obese Diabetic



Obesity → Hyperinsulinemia → Diabetes

What can be done to address the problem of pediatric obesity?

- Diet
- Lifestyle
- Pharmaceutical intervention?
  - Xenical?
  - Olean?
  - Others???

Xenical (orlistat)

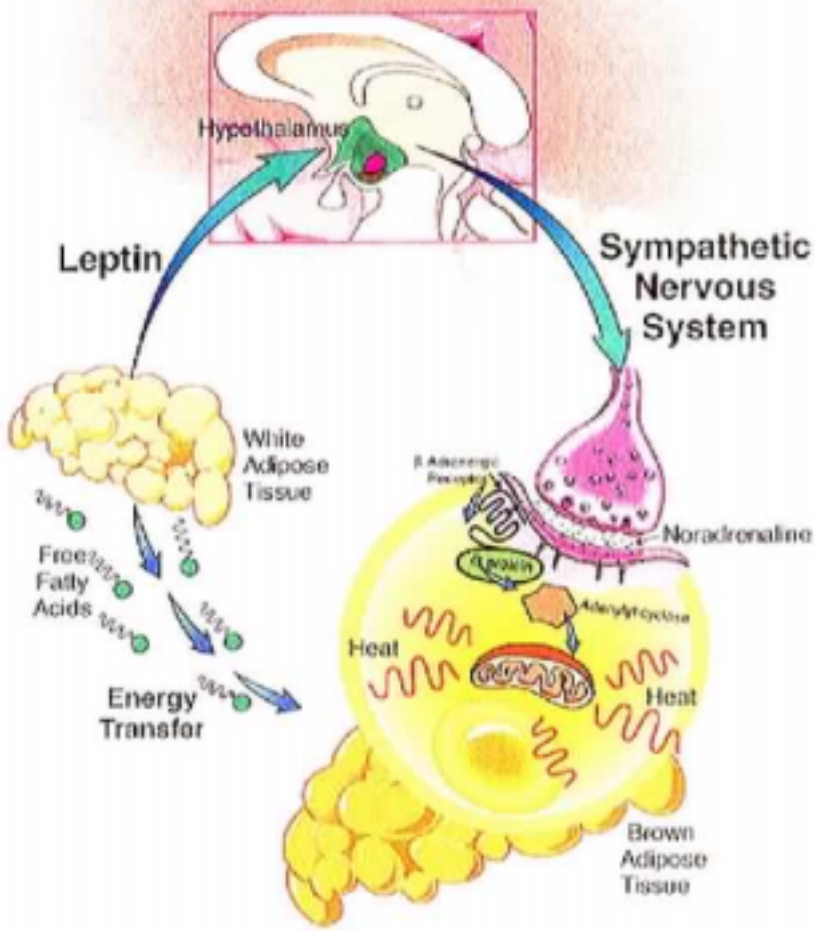
- Developed by Hoffmann-La Roche
- Approved in 1999 by FDA for obese patients with BMI > 30
- Inhibits activity of pancreatic lipase
- Decreases fat-soluble vitamin and carotenoid absorption

Olean (olestra)

- Developed by Procter & Gamble
- Approved in 1995 by FDA for use in snack foods
- BUT interferes with fat-soluble vitamin absorption
- Decreases blood levels of carotenoids (which decrease 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?



The fat cell as a dynamic endocrine tissue. Free fatty acids (FFA) taken up by adipocytes may be stored as triglycerides or serve a "hormonal" role, activating nuclear receptors (PPAR-type) or other fatty acid binding proteins. Hydrolysis of stored lipids to FFA occurs through AR substypes and activation of protein kinase A (PKA) and hormone-sensitive lipase (HSL), while glucose uptake and lipid synthesis are mediated by the insulin receptor (Ins-R) and its intracellular machinery (IRS). Leptin, the project of the *ob* gene, and the cytokine TNF serve as hormonal signals secreted from adipocytes to control fat metabolism.

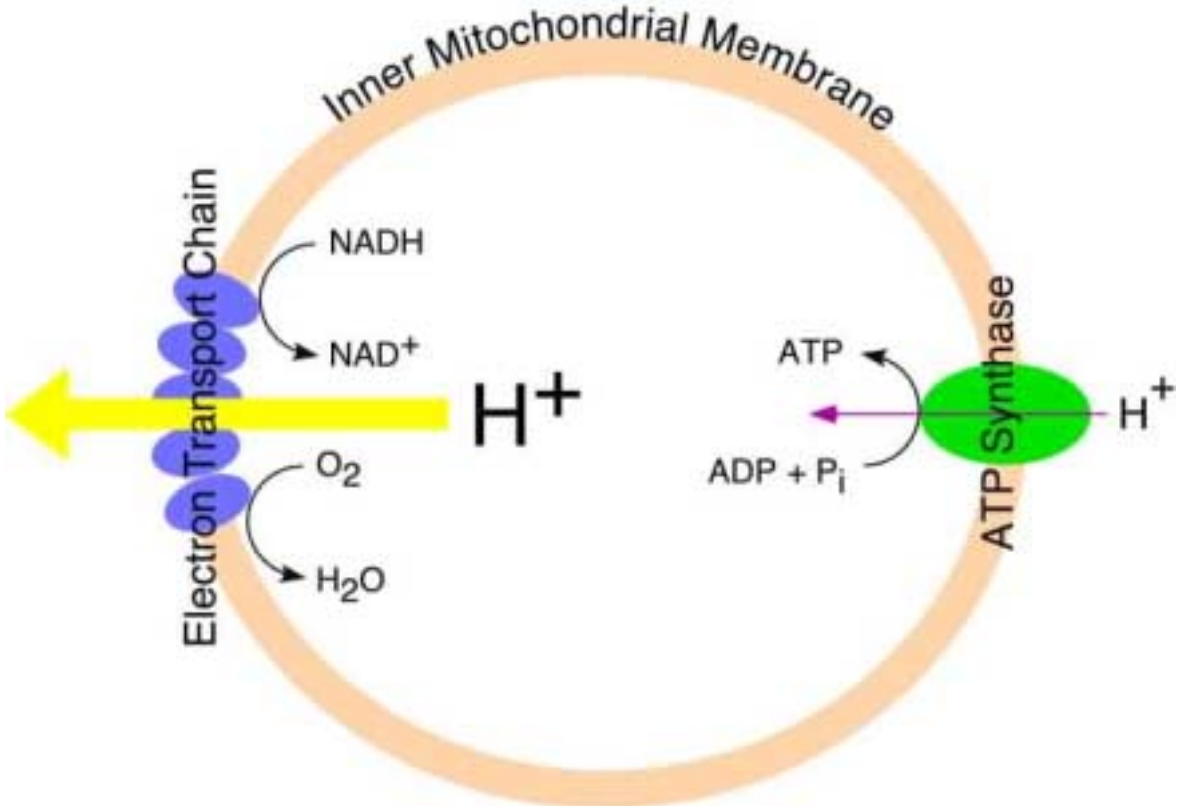
Nature 406 (2000) 415-418

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

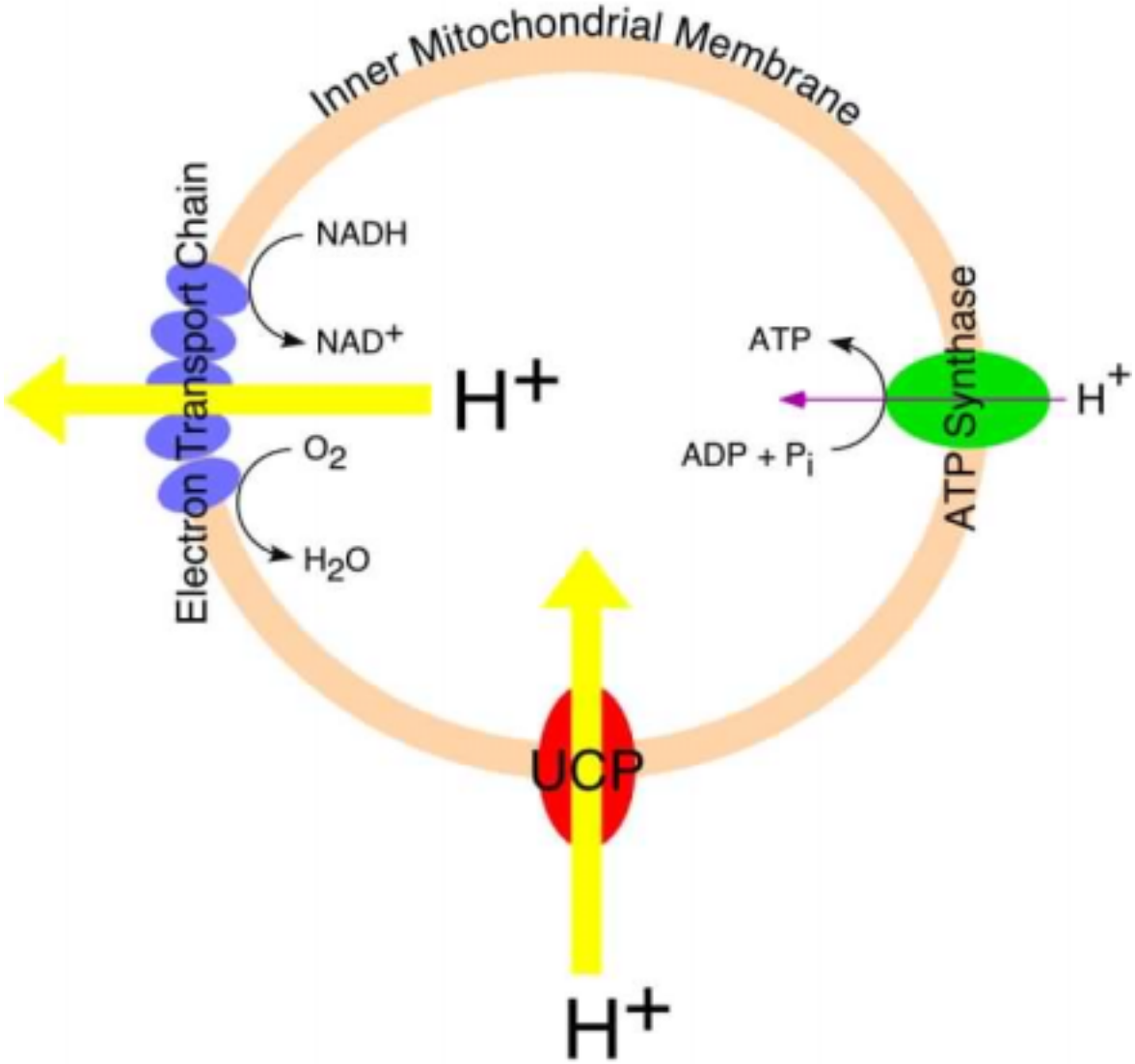
John C. Clapham*, Jonathan R. S. Arch*, Helen Chapman*, Andrea Haynes*, Carolyn Lister*, Gary B. T. Moore*, Valerie Piercy*, Sabrina A. Carter*, Ines Lehner*, Stephen A. Smith*, Lee J. Beeley••, Robert J. Godden§, Nicole Herrityk, Mark Skehel¶, K. Kumar Changani#, Paul D. Hockings#, David G. Reid#, Sarah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

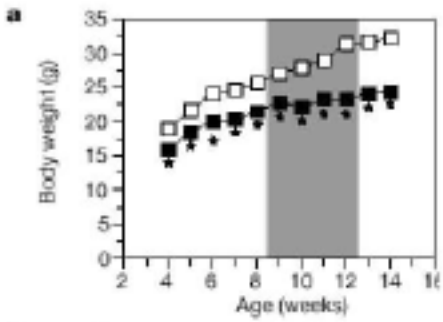


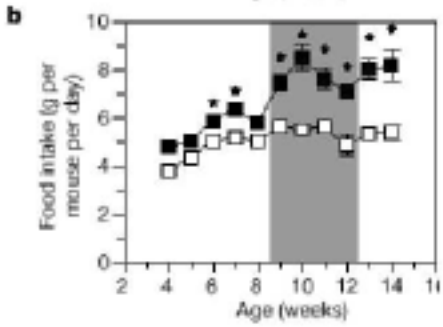
Uncoupling Protein

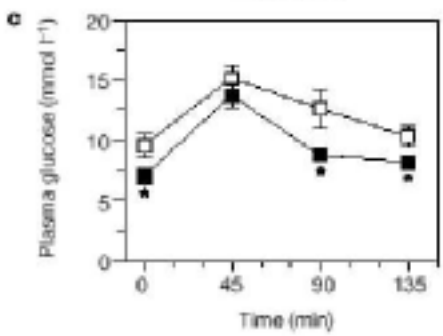


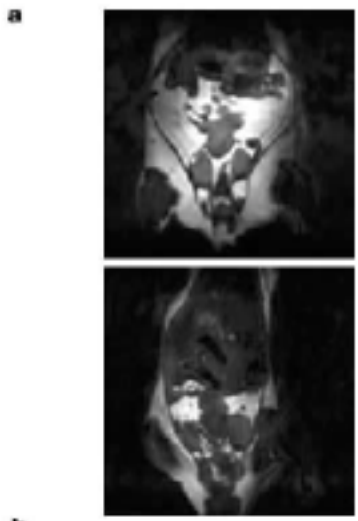
White = Control Mice

Black = Treated Mice



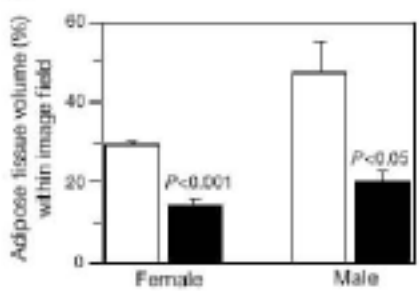






Control

Treated



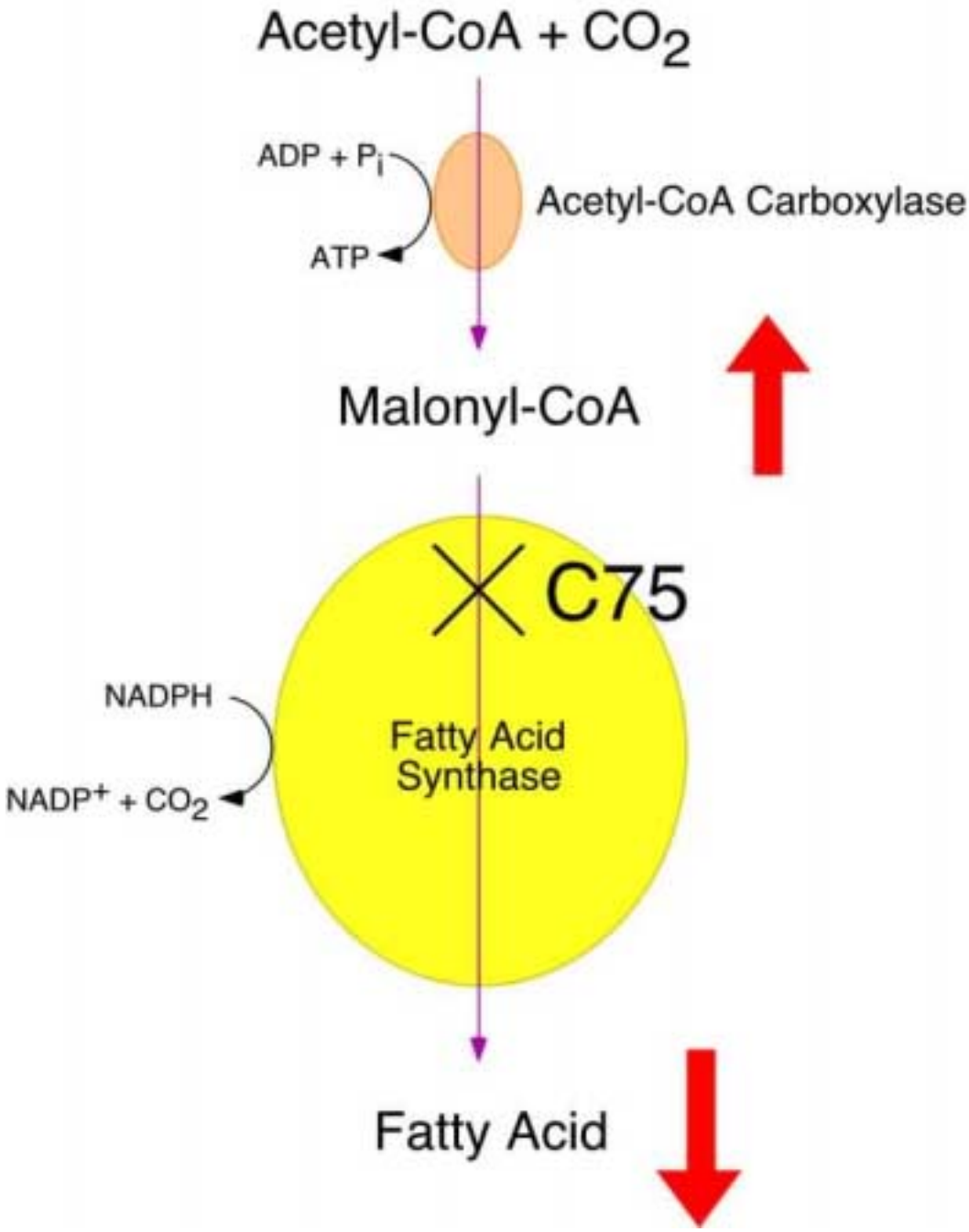
Science 288 (2000) 2379-2381

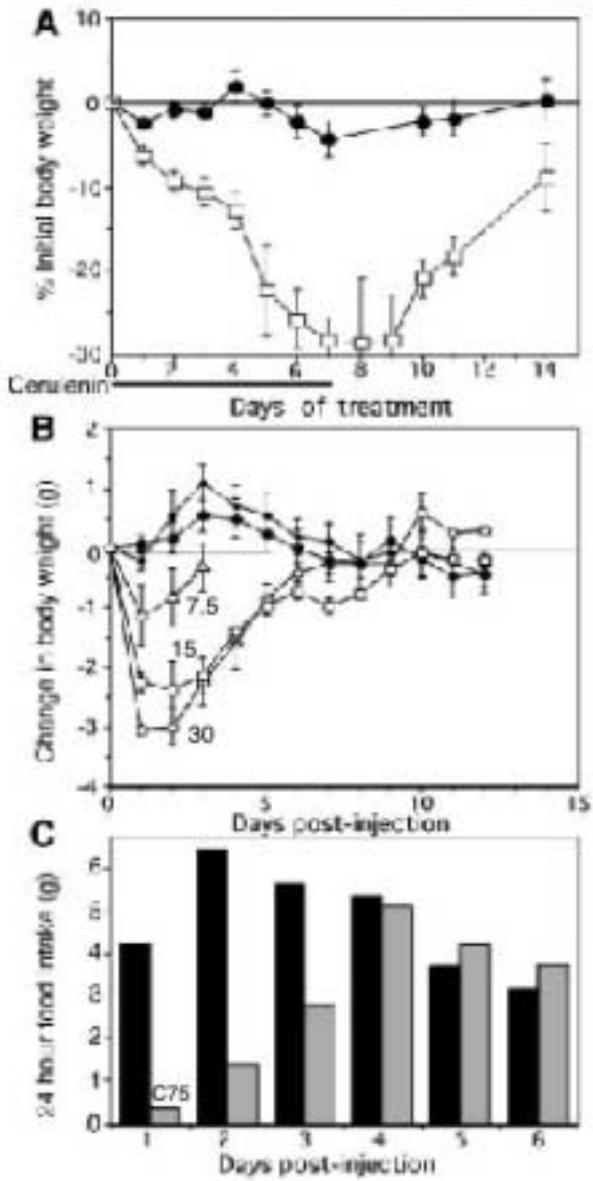
Reduced Food Intake and Body Weight in Mice Treated with Fatty Acid Synthase Inhibitors

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

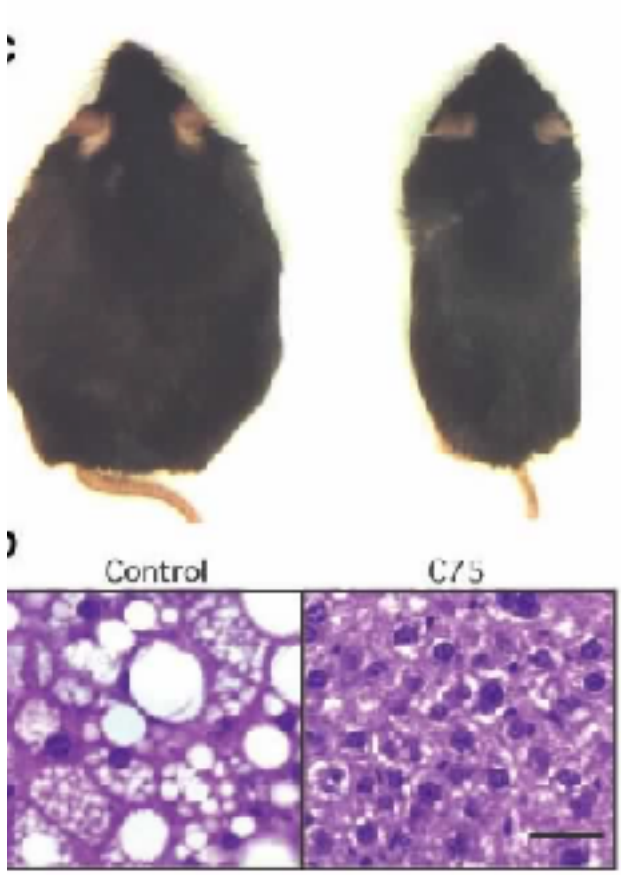
With the escalation of obesity-related disease, there is great interest in defining the mechanisms that control appetite and body weight. We have identified a link between anabolic energy metabolism and appetite control. Both systemic and intracerebroventricular treatment of mice with fatty acid synthase (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.

FAS Inhibitors





After 14 days of treatment



Tissue sections of liver