

## Section 2: Inhibition of Lipogenesis

### Overview

By inhibiting the actions of ATP-citrate lyase, HCA reduces the availability of acetyl-CoA the building block for fatty acid and cholesterol synthesis. The reduction in cholesterol synthesis tends to be greater than the reduction in fatty acid synthesis because sterols require the availability of acetyl units beyond those typically already present in the cytosol. Any reduction in fatty acid synthesis leads to a reduction in the production of triglycerides, the primary fat produced from carbohydrate calories. HCA may also cause the body to remove some already circulating low-density lipoprotein (LDL) from the blood.

Recent human trials (2003) have shown that supplementation with HCA can significantly improve blood lipid profiles. In that study, total cholesterol, LDL and triglycerides levels were reduced by 6.3%, 12.3% and 8.6% respectively, while HDL and serotonin levels increased by 10.7% and 40%, respectively. Body weight and BMI were reduced by 6.3% respectively, while food intake was reduced by 4%.

This confirms the results of animal studies that showed HCA induced reductions in triglycerides, cholesterol, food consumption and weight gain. Results in animal trials varied, but reductions in lipid production generally varied from 40 to 70% for periods of between 8 and 12 hours, but always less than 24 hours. However, experimental evidence indicates that HCA will not influence the actual lean to fat ratio in those cases in which this condition is of true genetic origin. Moreover, the inhibition of lipogenesis is reduced or reversed with diets high in fats or alcohol.

### HCA improves blood lipid profiles

#### Human *in vivo* study:

“High levels of total cholesterol, LDL cholesterol and triglycerides, as well as low levels of HDL cholesterol, are all risk factors for cardiovascular diseases, diabetes and stroke. The current study shows that supplementation with HCA-SX (brand leading HCA product) ... significantly improves blood lipid profiles.

Harry G. Preuss, Debasis Bagchi, Manashi Bagchi, C.V. Sanyasi Rao, S. Satyanarayana, Dīpak K. Dey 2003. **Efficacy of a novel, natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX, niacin bound chromium and *Gymnema sylvestre* extract in weight management in human volunteers: A pilot study.** Nutrition Research 24 (2004) 45-58

### **HCA inhibits Fatty Acid and Cholesterol Production**

#### ***In vivo* Study:**

“When the dose of (-)-hydroxycitrate was 1 mmole per kg of body weight the inhibition of fatty acid synthesis was about 75%.”

Lowenstein, John M. (1971). **Effect of (-)-hydroxycitrate on fatty acid synthesis by rat liver *in vivo***. The Journal of Biological Chemistry 246, 3 (February 10, 1971) 629-632

#### **Perfusion Experiment:**

“Fatty acid and cholesterol synthesis were inhibited in a similar manner by different (-)-hydroxycitrate concentrations. As *in vivo*, this compound appears to only partially inhibit fatty acid synthesis in the perfused organ.

The similarity of the (-)-hydroxycitrate effect on cholesterol and fatty acid synthesis is suggestive of a common mechanism of inhibition, e.g. lowering of the cytoplasmic acetyl-CoA level. This assumption requires that both effects be abolished by replenishment of the acetyl CoA pool by exogenous acetate. While this was verified for fatty acid synthesis, 3H- incorporation into cholesterol was not normalized by acetate addition.”

Barth, C., J Hackenschmidt, H. Ullmann, and K Decker (1972). **Inhibition of cholesterol synthesis by (-)-hydroxycitrate in perfused rat liver. Evidence for an extramitochondrial mevalonate synthesis from acetyl coenzyme A**. FEBS Letters 22, 3 (May 1972) 343-346

### **HCA encourages the Re-uptake and Catabolism of LDL Cholesterol**

#### ***In vitro* study:**

“The most significant finding in the present work is that overnight exposure Hep G2 cells to the ATP-citrate lyase inhibitor (-)-hydroxycitrate results in an up-regulation of LDL receptor activity and LDL-receptor –dependent LDL catabolism

Berkhout, Theo A., Louis M. Havekes, Nigel J. Pearce and Pieter H. E. Groot (1990). The effect of (-)-hydroxycitrate on the activity of low-density-lipoprotein receptor and 3-hydroxy-3-methylglutaryl-CoA reductase levels in the human hepatoma cell line Hep G2. Biochemistry Journal 272, 1 (1990) 181-186.

### **Effects of Acute and Chronic Oral Administration of HCA on Lipid Levels in the Rat**

#### ***In vivo* study:**

“Oral administration of (-)-hydroxycitrate depressed significantly the *in vivo* lipogenic rates in a dose dependent manner in the liver, adipose tissue and small intestine. The hepatic inhibition was significant for the 8hr. period, when control animals demonstrated elevated rates of lipid synthesis. The kinetics of this reduction of *in vivo* hepatic lipogenesis were identical after acute or chronic administration of.”

Sullivan Ann C., Joseph Triscari, James G Hamilton, O. Neal Miller, and Victor R. Wheatley (1974a). **Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat: I Lipogenesis**. Lipids 9, 2 (1974) 121-128.

### **Effects of Alcohol and Fat Consumption upon HCA's Actions**

#### **Perfusion Experiment:**

“No hydroxycitrate inhibition of acetate or ethanol incorporation [into fatty acid synthesis] was observed”

Brunengraber, Henri and John M. Lowenstein (1973). Effect of (-)-hydroxycitrate on ethanol metabolism. FEBS Letters 36, 2 (October 1973) 130-132.

### **Effects of HCA on Genetic and Experimentally-Induced Obesity**

#### ***In vivo study:***

The feasibility of treating obesity by metabolic regulation has been explored in the present study by examining the effects of (-)-hydroxycitrate on three types of experimentally induced obesity in the rodent. In each model, the mature rat, the GTG-induced [goldthioglucose] obese mouse, or the VMH [ventromedial hypothalamic] lesioned obese rat, the chronic oral administration of (-)-hydroxycitrate reduced significantly food consumption and weight gain. Analyses of body composition of the mature rats treated with (-)-hydroxycitrate revealed a significant reduction in total body lipid levels and no change in total body protein or liver lipid content”

Sullivan Ann C. and Joseph Triscari (1977a). **Metabolic regulation as a control for lipid disorders . I. Influence of (-)-hydroxycitrate on experimentally induced obesity in the rodent.** The American Journal of Clinical Nutrition 30, 5 (May 1977) 767-776

#### ***In vivo study:***

(-)-Hydroxycitrate reduced serum triglyceride levels and hepatic lipogenic rates equivalently in the Triton treated and non-treated rats.”

Sullivan Ann C., Joseph Triscari, and H.E. Spiegel (1977b). **Metabolic regulation as a control for lipid disorders. II. Influence of (-)-hydroxycitrate on genetically and experimentally induced hypertriglyceridemia in the rat.** The American Journal of Clinical Nutrition 30, 5 (1977) 777-784.

#### ***In vivo study:***

“The results of this study indicate that the [Zucker fa/fa female genetically] obese rat, despite a substantial reduction in body weight produced by (-)-hydroxycitrate, still defends its obese body composition.”

Greenwood, M.R.C., M.P. Cleary, R Gruen, D Blase, J.S. Stern, J. Triscari, and A.C. Sullivan (1981). Effect of (-)-hydroxycitrate on development of obesity in the Zucker obese rat. American Journal of Physiology 240, 1 (1981) E72-E78.

## Articles

Harry G. Preuss, Debasis Bagchi, Manashi Bagchi, C.V. Sanyasi Rao, S. Satyanarayana, Dipak K. Dey 2003. **Efficacy of a novel, natural extract of (-)-hydroxycitric acid (HCA-SX) and a combination of HCA-SX, niacin bound chromium and *Gymnema sylvestre* extract in weight management in human volunteers: A pilot study.** Nutrition Research 24 (2004) 45-58

Sullivan Ann C., Joseph Triscari, James G Hamilton, O. Neal Miller, and Victor R. Wheatley (1974a). **Effect of (-)-hydroxycitrate upon the accumulation of lipid in the rat: I Lipogenesis.** Lipids 9, 2 (1974) 121-128.

Sullivan Ann C. and Joseph Triscari (1977a). **Metabolic regulation as a control for lipid disorders . I. Influence of (-)-hydroxycitrate on experimentally induced obesity in the rodent.** The American Journal of Clinical Nutrition 30, 5 (May 1977) 767-776

Sullivan Ann C., Joseph Triscari, and H.E. Spiegel (1977b). **Metabolic regulation as a control for lipid disorders. II. Influence of (-)-hydroxycitrate on genetically and experimentally induced hypertriglyceridemia in the rat.** The American Journal of Clinical Nutrition 30, 5 (1977) 777-784.

Brunengraber, Henri, Mirelle Boutry, and John M. Lowenstein (1978). **Fatty acid, 3-B-hydroxysterol, and ketone synthesis in the perfused rat liver: Effects of (-)-hydroxycitrate and oleate.** Eur. J. Biochem., #2, (1978) 373-384.

Greenwood, M.R.C., M.P. Cleary, R Gruen, D Blase, J.S. Stern, J. Triscari, and A.C. Sullivan (1981). **Effect of (-)-hydroxycitrate on development of obesity in the Zucker obese rat.** American Journal of Physiology 240, 1 (1981) E72-E78.