Fatty Acid Synthase Inhibitors Reduce Food Intake and Body Weight

A review of: Loftus TM, Jaworsky DE, Frehywot GL, Townsent CA, Ronjnett GV, Lane DM Kuhajda FP 2000 Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. Science 288:2379–2381

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WITH OVER 10% of children in the United States obese, and an additional 15% overweight (1), the promise of a new potential therapeutic target for obesity treatment is exciting. Researchers at The Johns Hopkins School of Medicine have recently announced the discovery of a new appetite and body weight regulation pathway in mice (2). A research team led by Francis P. Kuhajda examined the effects of two inhibitors of fatty acid synthase (FAS), an enzyme that aids in the synthesis of long-chain fatty acids from acetyl-CoA and malonyl CoA. Mice given the FAS inhibitors demonstrated a 95% inhibition of fatty acid synthesis. Food intake was reduced by approximately 90% over the first 24 h, and body weight decreased by approximately 30% over 1 wk. One-week treatment with FAS inhibitors also dramatically normalized the fatty liver in ob/ob mice. The researchers hypothesize that FAS inhibitors may act directly on the appetite centers in the brain, mediated by neuropeptide-Y. Increased levels of malonyl CoA, a precursor of fatty acid synthesis, may also decrease nutrient mediated insulin secretion.

This research may provide an important clue into the complex mechanism of appetite suppression and weight control; however, the molecular biology of obesity in humans remains poorly characterized. Hundreds of putative appetite and weight regulating hormones have been described in animal models and humans (3). Although it is likely that the same broad mechanisms that regulate appetite in animals apply to humans, the importance of individual neurotransmitters may vary considerably. At this time, the role of individual genes, hormones, and neurotransmitters in determining obesity in humans remains unknown. Although the recent discovery of the hormone leptin has promised to revolutionize the field of obesity, the role of leptin and the leptin receptor to human obesity also remains controversial. To date, no specific enzymatic abnormality has been described in the majority of obese humans.

Childhood obesity remains primarily a family problem. Genetic and pharmaceutical advances will not affect a child's preferences for Big Macs over broccoli, nor will they encourage physical activity in children who spend 4 to 6 h in front of the television or computer each day. Parents play a critical role in food purchasing and preparation, in addition to controlling the variety and quantity of food offered. Access to high calorie snacks, soda, and fast food is also a family issue. Parents provide encouragement or discouragement of physical activity, and they also provide transportation and access to recreational activity. Childhood food preferences are also greatly influenced by the food choices and eating habits of their parents. In addition, children raised in highly stimulating, nurturing environments are less than one-half as likely to become obese as children raised in less stimulating environments (4). Therefore, the findings that fatty acid synthase (FAS) inhibitors may regulate appetite and decrease weight in animal models is interesting and may be important, but undue optimism for a quick fix to the obesity epidemic is not warranted.

1. Troiano R, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL 1995 Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys 1963 to 1991. Arch Pediatr Adolesc Med 1085–1091
2. Loftus TM, Jaworsky DE, Frehywot GL, Townsent CA, Ronjnett GV, Lane DM Kuhajda FP 2000 Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. Science 288:2379–2381
3. Chagnon YC, Peruse L, Weisnagel SJ, Rankinen T, Bouchard C 2000 The human obesity gene map: the 1999 update. Obesity Res 8:89–117
4. Strauss RS, Knight J 1999 The role of the home environment and socioeconomic factors in the development of childhood obesity. Pediatrics 103:e85

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