Journal of
Medicinal
Chemistry

Volume 49, Number 14 July 13, 2006

Miniperspectives: Antiobesity Pharmacotherapy

Approaches to Antiobesity Therapy. An Introduction

Michael J. Bishop[†]

GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, North Carolina 27709

Received June 15, 2005

Many researchers in industry, academia, and the clinical arena are grappling with how to effectively approach the challenge of reducing obesity and its health risks because the levels of obesity have increased significantly in developed countries over the past 2 decades. Reports from the Centers for Disease Control (CDC) illustrate this effectively, showing a dramatic increase in the number of obese adult Americans since 1991 (Figure 1).[1] Obesity, characterized by an excess of adipose tissue relative to lean mass, is associated with numerous negative health consequences, including heart disease, type 2 diabetes, osteoarthritis, hypertension, stroke, sleep apnea, and certain types of cancer. This series of Miniperspectives is intended to provide a glimpse into some of the more active and exciting pharmacological research approaches to discovering treatments for the disease of obesity.

On a simple level we can consider obesity the result of a long-term energy imbalance. When energy intake exceeds energy output or expenditure, the excess calories are stored as adipose tissue, resulting, over time, in obesity. However, in the following manuscript in this series, designed to provide an overview of obesity, Dr. George Bray of the Pennington Biomedical Research Center describes an epidemiological model to help us better understand the disease of obesity. Dr. Bray has been involved in metabolic disease research for over 40 years and is one of the founders of NAASO, the North American Association for the Study of Obesity. He is uniquely qualified to define the disease of obesity, to describe the contributing factors to the obesity epidemic, and to outline the current state of clinical treatment.

Clinical management of obesity seeks to return the body weight of obese patients to a healthier level, and current therapies include behavioral, dietary, pharmacological, and surgical approaches. Surgery is clearly the most effective therapy at this time for significant, rapid, and sustained weight loss. However, these treatments have short-term and long-term risks associated with the procedures, including reported early mortality rates ranging from 0.3% to 1.9%.[2] At the present time, only two drugs are approved by the U.S. Food and Drug Administration for the long-term treatment of obesity: the dual serotonin−norepinephrine reuptake inhibitor sibutramine (Meridia) and the pancreatic lipase inhibitor orlistat (Xenical). While these agents do show clinical efficacy, they both have some tolerability or safety concerns.[3] There is a tremendous opportunity to make a significant, positive impact on the health and lives of obese people through the discovery and development of additional drug therapy options. The molecular entities that are discussed as possible targets for antiobesity therapy in the following Miniperspectives (CB-1, MCH-1, 5-HT_{2C}, and MC4 receptors) are all G-protein-coupled receptors. Furthermore, these receptors are found in high levels in the central nervous system and have been associated with alteration of energy intake behavior, although some of these targets are also found in the periphery at significant levels and may have effects on body weight via alteration of energy expenditure as well.

The most likely class of compounds to make an impact in the near term is the cannabinoid-1 receptor (CB-1) antagonists, most immediately through Sanofi's phase III compound rimonabant (Accomplia). CB-1 is a G-protein-coupled receptor that is definitely involved in feelings of hunger and subsequent food intake and appears to be involved in additional pathways that affect energy expenditure. Several other pharmaceutical companies are also advancing promising CB-1 antagonists in clinical trials, including Solvay Pharmaceuticals. Dr. Jochen Antel, director of metabolic disease drug discovery at Solvay,

[†] Phone: 919-483-9581. Fax: 919-315-0430. E-mail: michael.j.bishop@gsk.com.

10.1021/jm0582367 CCC: $33.50
Published on Web 06/17/2006

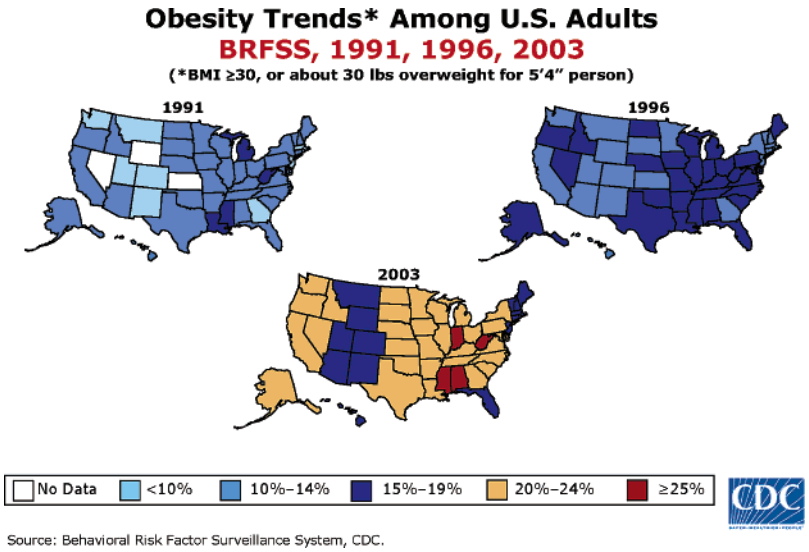

Figure 1. Obesity trends, reprinted from the public domain from the Behavioral Risk Factor Surveillance System, Center for Disease Control.

has written a Miniperspective focused on recent developments in the CB-1 antagonist field.

Another area of considerable research activity is the identification of melanin-concentrating hormone-1 receptor (MCH-1R) antagonists. Patent applications from many pharmaceutical companies describing small-molecule antagonists of MCH-1R have appeared over the past 2 years, and considerable clinical activity is expected to be ongoing or imminent. For this Miniperspective series, Dr. Tony Handlon of GlaxoSmithKline evaluates the potential of MCH-1R antagonists as antiobesity agents.

Turning to agonists of G-protein-coupled receptors, activation of the serotonin receptor 5-HT_{2C} has been an area of keen interest at several pharmaceutical companies. Fenfluramine, alone and especially as part of the "phen-fen" combination (with phentermine), provided great hope for obesity pharmacotherapy in the 1990s because many patients experienced significant weight loss while on this medication. However, serious adverse events associated with fenfluramine therapy, most notably heart valve changes, led to the removal of this agent from the market. There is evidence linking the exciting weight loss effects of fenfluramine with activation of the 5-HT_{2C} receptor, and researchers have been interested in discovering drugs that have the potential of fenfluramine-like efficacy without the adverse effects. In this Miniperspective series, Dr. Björn Nilsson of Biovitrum AB provides a rich review of 5-HT_{2C} receptor research based on his extensive experience in the area.

Finally, the melanocortin-4 receptor (MC4R) pathway has perhaps the strongest support for a key role in energy regulation of any target lacking clear clinical validation, via human and nonhuman genetic evidence and considerable pharmacological data. Loss of function mutations lead to severe obesity, and activation of MC4R in animal models can cause food intake reduction and body weight loss. While there has been widespread enthusiasm for MC4R research, the identification and development of high-quality agonist drug candidates have proven to be difficult for many, as demonstrated by the limited amount of clinical activity. Researchers at Merck have been leaders in the discovery of both peptidic and nonpeptidic MC4R agonists, and Dr. Ravi Nargund and colleagues at Merck have written an informative Miniperspective on this topic to complete this series.

The four molecular targets reviewed in these Miniperspectives represent only a handful of the exciting avenues of antiobesity research currently being investigated. In addition to other interesting central nervous system targets, there are a number of predominantly peripheral targets, such as those involved in fatty acid synthesis, fatty acid oxidation, fat storage, and adipocyte regulation that are not discussed in this series of Miniperspectives. Treatment of obesity as a component of metabolic syndrome is also worthy of in-depth discussion. Additionally, combinations of drugs will certainly be important in the management of obesity, just as they are in the management of diabetes and hypertension. Clearly there is plenty to review in future series!

This Miniperspective series is derived from an antiobesity symposium sponsored by the Division of Medicinal Chemistry at the 227th National Meeting of the American Chemical Society in Philadelphia in 2004. As an organizer of this symposium, I was recruited to help identify topics and authors for this series. The authors of this series have prepared excellent introductions to some exciting targets that should stimulate further innovative research in the area of antiobesity therapy.

References

(1) *Overweight and Obesity: Obesity Trends: U.S. Obesity Trends 1985−2003*; Behavioral Risk Factor Surveillance System, Centers for Disease Control and Prevention: Atlanta, GA, 2005.

(2) Snow, V.; Barry, P.; Fitterman, N.; Qaseem, A.; Weiss, K. Pharmacological and Surgical Management of Obesity in Primary Care: A Clinical Practice Guideline from the American College of Physicians. *Ann. Intern. Med.* **2005**, *142*, 525−531.

(3) Li, Z.; Maglione, M.; Tu, W.; Mojica, W.; Aterburn, D.; Shugarman, L.; Hilton, L.; Suttorp, M.; Solomon, V.; Shekelee, P. G.; Morton, S. C. Meta-Analysis: Pharmacologic Treatment of Obesity. *Ann. Intern. Med.* **2005**, *142*, 532−546.

JM0582367