Available online at www.sciencedirect.com
ScienceDirect
Pharmacology & Therapeutics 117 (2008) 105–122
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: J.L. Katz

The development of tolerance to drugs that suppress food intake

John D. Fernstrom [a,b,*], SuJean Choi [a,c]

[a] Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213, United States
[b] Department of Pharmacology, University of Pittsburgh, Pittsburgh, PA 15213, United States
[c] Department of Psychology, University of Pittsburgh, Pittsburgh, PA 15213, United States

Abstract

Appetite suppressants have been available as weight-reducing aids for over 50 years. The first discovered was amphetamine, which was potent, but possessed undesirable side effects (it is a stimulant and elevates blood pressure). Subsequently, a variety of appetite drugs was developed, all structurally related to amphetamine, but mostly lacking unwanted side effects. Until recently, fenfluramine (FEN) was the most widely used; presently, sibutramine is the most commonly used appetite suppressant. While these appetite suppressants are effective at reducing hunger and food intake when given as a single dose or for short periods of time, their effectiveness diminishes when administered chronically. The biological mechanisms underlying this tolerance have not been carefully studied, but many possibilities have been identified, including the down-regulation in brain of neurotransmitter receptors that might mediate the action of these drugs and adaptive responses of the appetite control circuitry in brain. To date, however, few studies have examined these possibilities in any detail. This article focuses on the question of why appetite suppressants lose efficacy, when given chronically, because this issue is important to the development of the next generation of appetite suppressants. Chronic efficacy should be an issue studied relatively early in the drug development process. This issue is of particular relevance, since obesity treatment is now recognized as a long-term, not a short-term, process. If appetite suppressants are to become a more important tool in obesity treatment, agents that do not lose efficacy when administered for extended periods of time must be identified.

Keywords: Appetite suppressants; Food intake; Tolerance; Obesity; Human; Rodents

Abbreviations: 5HT, serotonin; αMSH, α-melanocyte-stimulating hormone; AgRP, agouti-related protein; BMI, body mass index; BNST, bed nucleus of the stria terminalis; CART, catecholamine and amphetamine related transcript; CCK-8, cholecystokinin octapeptide; CRF, corticotrophin-releasing factor; FEN, fenfluramine; LHSS, lateral hypothalamic self-stimulation; MCH, melanin-concentrating hormone; mCPP, *m*-chlorophenylpiperazine; mRNA, messenger ribonucleic acid; MTII, melanotan II; NPY, neuropeptide Y; NST, nucleus of the solitary tract; PBN, parabrachial nucleus; POMC, proopiomelanocortin; pPVN, parvocellular paraventricular nucleus.

Contents

* Corresponding author. UPMC/Western Psychiatric Institute & Clinic, Room 1620, 3811 O'Hara Street, Pittsburgh, PA 15213, United States. Tel.: 412 246 5297; fax: 412 246 6470.
E-mail address: fernstromjd@upmc.edu (J.D. Fernstrom).

0163-7258/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2007.09.001

1. Introduction

Appetite suppressants are drugs that help overweight and obese patients lose weight. They fit within 1 of the 3 clinical approaches currently used to control and reduce body weight: lifestyle counseling, pharmacotherapy, and surgery. Interest in promoting weight loss in obese patients is at an all-time high, driven by the alarming recent increase in the incidence of obesity in developed countries and convincing evidence that, as body weight rises, the incidence of certain life-threatening diseases increases. Such diseases include diabetes (type 2), cardiovascular disease (heart attack, stroke), cancer, and bone and joint disorders (NHLBI Obesity Education Initiative Expert Panel on the Identification, 1998; Must et al., 1999). In obese individuals with 1 or more obesity-related illnesses, treatments that lower body weight can moderate or eliminate disease and disease risk (Neter et al., 2003; Sjöström et al., 2004; Fernstrom et al., 2006). As a consequence, interest in the improvement of weight-loss aids has increased, including the development of new drugs that lower body weight by reducing hunger (and thus food intake).

For appetite suppressants, the current generation of drugs is still the first generation. The same structural group of agents has been in use, with only occasional modification, for over 50 years (Silverstone, 1992). While some are potent in reducing hunger and food intake when initially administered, all lose their appetite-suppressing efficacy when taken for extended periods of time. This apparent tachyphylaxis is widely known, but not widely studied. Even with the recent explosion of new information regarding the structural and neurochemical organization of appetite control circuitry in brain (Schwartz et al., 2000; Berthoud, 2002; Broberger, 2005), this knowledge has not yet been applied to the exploration of the bases underlying this loss of efficacy. Moreover, as drug development programs are stimulated in their search for novel appetite suppressants, little regard appears to be given to this issue (Vickers & Dourish, 2004; Miller, 2005). The tolerance of appetite suppressants is an important therapeutic issue, since this drug class is important not only as a self-standing weight-loss treatment, but also as an adjunct to other treatments (e.g., lifestyle, surgery), wherein hunger increases as weight loss progresses, and a loss of dietary compliance can sabotage long-term success.

Hence, this article raises the issue for consideration in the hope that it will help to focus interest in the study of why appetite suppressants stop working with repeated administration and the development of new agents that lack this undesirable effect. In the article that follows, available evidence is reviewed, demonstrating that appetite suppressants induce weight loss for only a limited period of time when administered chronically, that the effect is likely to be related to a loss of efficacy in suppressing appetite, and that new biological agents/drugs, as well as the first generation appetite suppressants, show this effect. The problem is thus not avoided simply by moving to novel types of drugs, at least thus far suggesting that some general property of the appetite control circuit may be at the heart of the problem. To discuss this information, it is first important to understand the problem in the species of greatest interest, humans. Data in animal models will then be discussed. Finally, consideration will be given to mechanisms by which appetite suppressants may initially reduce food intake and how alterations in these mechanisms may occur with long-term appetite suppressant use and contribute to the loss of efficacy seen with these drugs.

2. Weight loss after long-term use of appetite suppressants in humans: the record

Appetite suppressants reduce short-term hunger and food intake in humans (Shoulson & Chase, 1975; Blundell & Halford, 1998); food intake can be monitored directly in such controlled circumstances. However, long-term food intake cannot be measured directly, due to cost and inconvenience. Moreover, intake data supplied by the subjects cannot be used, since humans are not reliable reporters of what they eat (they underreport caloric consumption as can readily be verified, for example, using doubly labeled water; Schoeller, 1995; Blundell, 2000; Goris et al., 2000). Hence, long-term studies report the effects of appetite suppressants on body weight, an objective measure of energy balance, and assume that any change, if physical activity is roughly constant and a drug does not stimulate metabolism, will reflect a change in food (energy) intake.

There have been few chronic studies lasting more than 3–4 months, and these began to accumulate only around 1990. This fact may reflect an earlier, general feeling that appetite suppressants should be used on a limited basis for short periods of time, if at all (Guy Grand, 1987; Guy Grand et al., 1989; Silverstone, 1992; Weintraub, 1992). Fortunately, this perception has changed (Guy Grand et al., 1989; Weintraub, 1992). But while the pool of chronic studies is small, they are remarkably consistent in what they reveal. A long-term study of fenfluramine (FEN) in combination with phentermine offers a good example (Weintraub, 1992). FEN is primarily a serotonin (5HT)-releasing agent, and phentermine is a norepinephrine-releasing drug; both act in brain to suppress food intake (Sugrue, 1987). While this study lasted 4 years, the initial 6-month period reveals the typical response of body weight to an appetite suppressant (Fig. 1). The design called for an initial run-in period of 6 weeks, during which all subjects received diet and exercise training and behavioral modification