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business trends

Obesity: the fat lady sings?

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The Kalahari Desert is a barren wilderness almost devoid of food. One of the few plants hardy enough to survive there is a bright green cactus known as xhoba, or hoodia. The Kalahari is also home to the San bushpeople. This southern African tribe are hunter-gatherers, with a lifestyle that necessitates long and arduous treks across the desert in search of food. The San males use the hoodia cactus for sustenance while out in the desert, because its properties extend beyond simple nutrition. The desert is a fairly unlikely place to expect to find a cure for obesity, but it appears that hoodia could be just that.

Ethnopharmacology

The San hunters find that hoodia, when eaten even in small quantities, causes the sensation of hunger to cease. With ethnopharmacology growing in popularity as a source of drugs, it was only a matter of time before news of the more interesting properties of hoodia became known to researchers. After isolation by the South African Council for Scientific and Industrial Research (CSIR), the active compound was patented. Rights to the chemical, known as P57, were acquired by Phytopharm (UK), which specializes in therapeutic botanical compounds. P57 does not cause breakdown of fatty tissue, it is simply an appetite suppressant, markedly decreasing the calorie intake of treated patients. It is now under development by Phytopharm for the treatment of obesity and metabolic syndrome and, if approved, is set to become a blockbuster. It is also licensed to Unilever for development as a food ingredient. A proportion of the profits has been promised to the San, to provide job opportunities, scholarships and the right to grow hoodia themselves.

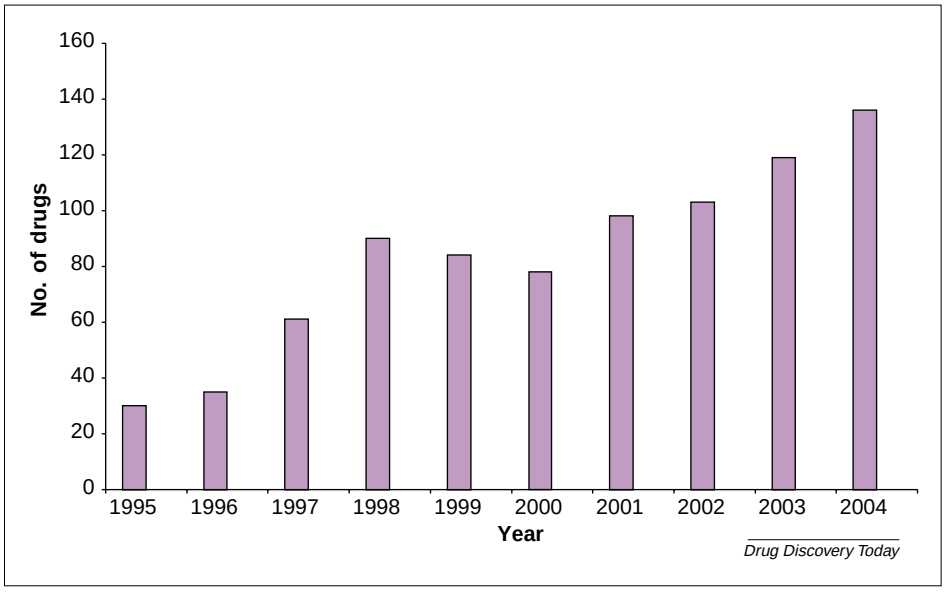

FIGURE 1

Appetite suppressant drugs in active development 1995–2004. Data courtesy of Pharmaprojects.

'Globesity'

The aetiology of obesity is regarded as complex, consisting of the interaction of a variety of genetic, metabolic, environmental and behavioural factors. More recently, a virus has been mooted as yet another causative possibility. Although widely regarded as a problem almost exclusively confined to the developed world (with its fast food and sedentary lifestyle), the obesity 'epidemic' is in reality sweeping inexorably through non-industrialized countries. The World Health Organization (WHO) points out that the prevalence of obesity is often increasing at a faster rate in developing countries than in the developed world – the phenomenon of 'globesity'.

A patient is diagnosed as obese if their Body Mass Index – defined as the weight of the patient (in kg) divided by the square of their height (in m) – is greater than 30 kg m^{-2}. With over 300 million adults worldwide meeting this criterion (a worldwide prevalence of >2%), it is perhaps unsurprising that the worldwide obesity market has been predicted to reach US$3.7 billion by 2008. The condition itself leads to an alarming range of further complications, either causing or exacerbating disorders such as diabetes mellitus, stroke, cancer, hypertension and atherosclerosis.

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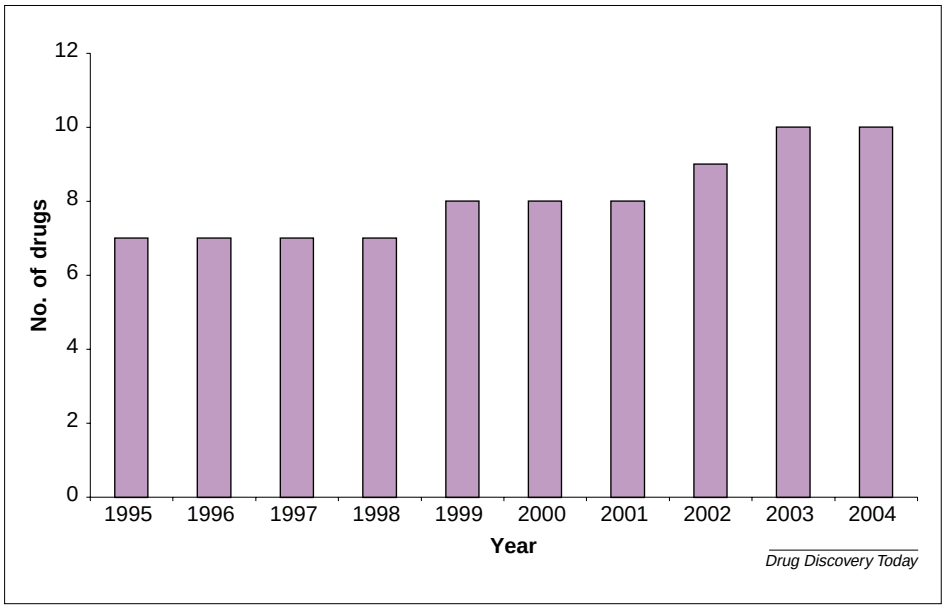

FIGURE 2

Launched appetite suppressant drugs (1995–2004). Data courtesy of Pharmaprojects.

These apparently disparate conditions often occur together, and are referred to by the blanket term 'insulin-related metabolic syndrome'.

Recent developments

Obesity is by no means a recent disease. During the 16th, 17th and 18th centuries, corpulence was entirely fashionable as evidence of one's prosperity. However, from the late Victorian period onwards, people have sought to control their expanding waistlines by any means possible, progressing from corsets to surgery to pharmacological agents. The development of obesity medication rapidly increased from 1995 to 1998 (Figure 1) as pharmaceutical companies attempted to meet the demand. A slight decline in the number of appetite suppressants in development from 1998 to 2000 is evident, coinciding with the decision made by the FDA in late 1997 to withdraw the appetite

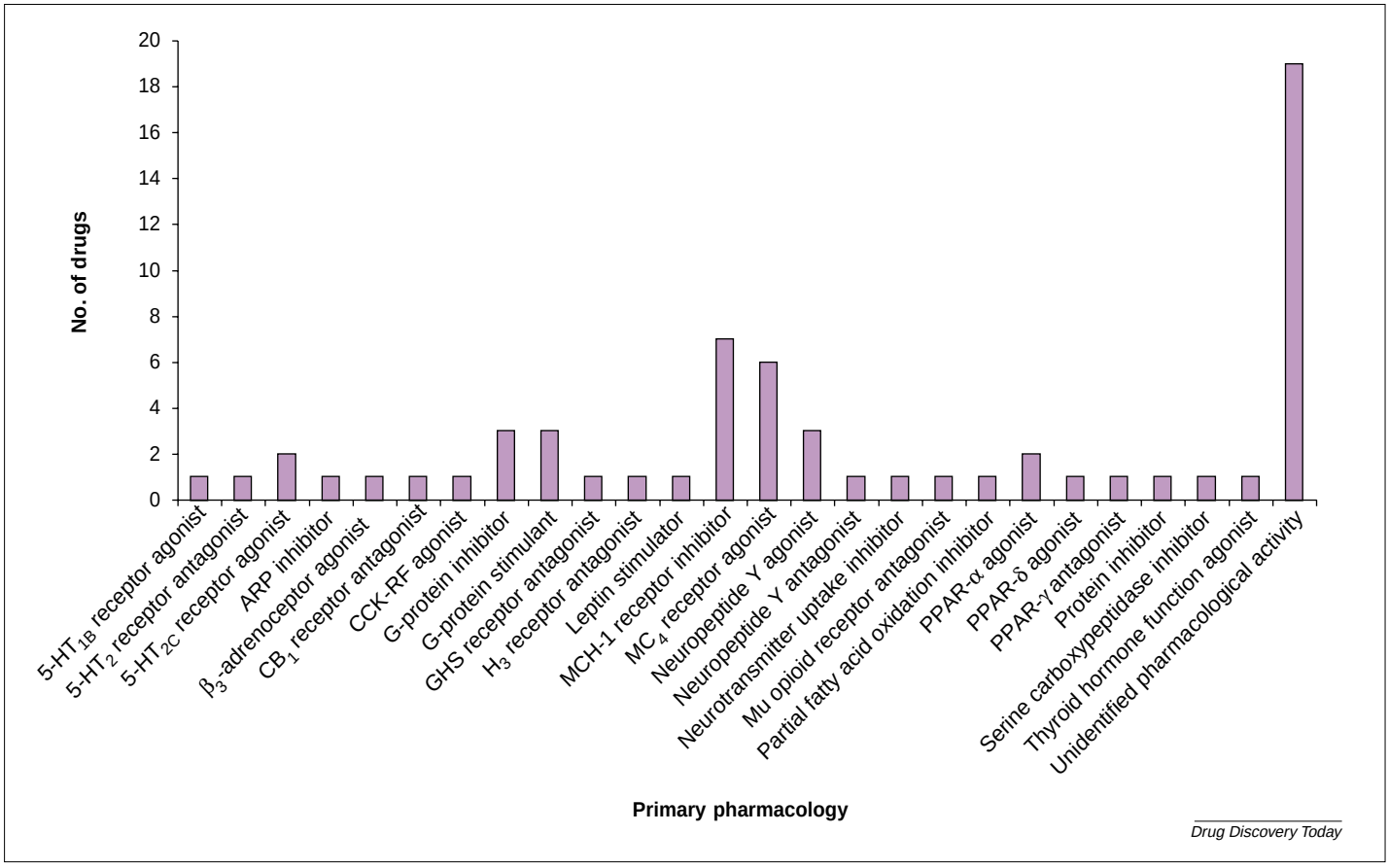

FIGURE 3

Pharmacological activities of appetite suppressants in preclinical development. Data courtesy of Pharmaprojects. Abbreviations: ARP, agouti-related protein; CB_1, cannabinoid 1; CCK-RF, cholecystokinin releasing-factor; GHS, growth hormone secretagogue; H, histamine; HT, hydroxytryptamine; MC-4, melanocortin-4; MCH-1, melanin-concentrating hormone-1; PPAR, peroxisome proliferator-activated receptor.

conference report

suppressants fenfluramine and dexfenfluramine. These drugs had been among the most widely prescribed medications for obesity when combined with phentermine. Known as 'fen-phen', their success appeared unassailable, but the combination was found to cause malfunction of the heart valves in approximately 30% of patients. After this setback, the number of appetite suppressants under development is again rising: development of obesity therapeutics has increased 453% over the past decade.

The more cautious increase of recent years could be the result of the regulatory difficulties observed with other launched anorectic drugs (Figure 2). Before its approval and launch as Meridia®, Abbott's sibutramine (a serotonin and norepinephrine reuptake inhibitor) had been rejected by the FDA's Endocrinologic and Metabolic Advisory Committee as a result of concerns that the potential risk of elevated blood pressure outweighed the benefits of weight loss; safety and efficacy issues were also raised in Europe, particularly in Belgium and Italy. Roche's widely launched orlistat (Xenical®) inhibits lipase, an enzyme found in the gastrointestinal tract that aids digestion of dietary fat. This results in a marked increase in the amount of triglycerides excreted in the faeces, rendering it unsuitable for treatment of patients with irritable bowel syndrome or Crohn's disease, and disagreeable for non-sufferers because it results in steatorrhoea.

Continuing research

Although obesity has existed since humans first developed agriculture (the earliest known representation of the human form is the Venus of Willendorf, a 25,000-year-old sculpture of an obese woman), it is only within the past half-century that it has become a widespread medical catastrophe. This is a consequence of advances in the treatment of more traditional killers (e.g. smallpox, cholera and tuberculosis), coupled with an ageing population, and thus it is only recently that weight loss has become vital for health, rather than stylistic, reasons. Because, at the molecular level, obesity does not have one simple, straightforward cause, it is difficult to know how to combat it pharmacologically. The pharmacological approaches through which the appetite suppressants currently in preclinical development mediate their effects are varied (Figure 3), with the pharmacologies of the largest proportion unknown. Many are psychologically active, with serotonin, neuropeptide Y and even cannabis receptor modifiers present.

The burgeoning market for these drugs and the vast sums of money at stake guarantee that research in this therapeutic area will not slow within the foreseeable future. The notion of a pill that will result in cessation of hunger, and hence easy weight loss, is an extraordinarily beguiling one. Unfortunately, all currently marketed anorectic drugs require dietary modification to have maximum effect with minimal side effects – patients treated with Xenical® must ensure that no more than 30% of the calories in their diets come from fat.

According to the WHO, over one billion adults worldwide are overweight. Nearly five million US adults used prescription weight-loss medication between 1996 and 1998, and half the population of the USA will be obese by 2030. Unless appetites are tamed by medication, or people finally learn to resist temptation, the future looks bleak.

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Glycomics: coming of age across the globe

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Post-translational modifications (PTMs) have been recognized as underlying much of the diversity of the human proteome superimposed on the relatively limited peptide sequence repertoire encoded by the genome [1]. Although comparatively simple PTMs, such as phosphorylation or acylation, have been targeted extensively for drug discovery, by far the greatest repertoire of structural and functional diversity on proteins is created by another process of PTM, known as glycosylation. Glycosylated proteins (glycoproteins) and other glycoconjugates occur in all compartments of the living cell, and carbohydrate structures are of particular importance on the cell surface, where they mediate fundamental processes underlying cell–cell and cell–matrix interactions, cell proliferation and infection. The science of biologically relevant complex carbohydrates has been unified under the term glycobiology [2].

In the USA, many glycobiologists are organized in the Society for Glycobiology (SfG), the annual meetings of which have

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