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A succulent cure to end obesity

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A novel compound derived from a South African succulent has shown promise as an appetite suppressant in clinical trials and could have potential as a new anti-obesity drug. This is good news at a time when obesity has become so prevalent that experts speak of an epidemic.

Obesity is a multifactorial disease. Although lifestyle factors have an important role in its development, individual differences in body weight could also depend on genetic factors [1]. Being overweight can have serious consequences, such as heart disease, diabetes, hypertension and osteoarthritis. It is estimated that these complications account for 5–10% of all health costs in EU countries [2]. Although the best approach to controlling weight is still a combination of a diet with fewer calories, increased physical activity and behaviour modification, there is a growing awareness that drug therapy should also play an important role in the management of obesity. However, treatment options are limited, and the currently available therapies come with their own risks (Box 1). Therefore, more drugs of a greater variety are warranted to help as many people as possible.

From the bush to the clinic

The compound P57 is derived from a ~2 m high succulent of the *Hoodia* family (Fig. 1). The plant grows in the arid Kalahari desert on the border of South Africa and Namibia and has been used by the Xhomani bushmen, a people indigenous to the region, for thousands of years as a bush food during hunting trips. In the 1960s, the Xhomani disclosed the plant's secrets to the South African army. The Council for Scientific and Industrial Research (CSIR), a statutory scientific research council in South Africa, then started to investigate the plant's effects: they demonstrated in animal studies that an extract from the plant was highly effective in reducing weight. In 1997, the CSIR approached Phytopharm (Godmanchester, UK), a company developing drugs derived from plants (botanicals), to collaborate in the development of the active ingredient, P57, into a prescription drug. The CSIR have retained the marketing rights in South Africa; according to Richard Dixey, CEO at Phytopharm, the research council is currently negotiating a profit-sharing agreement with the Xhomani people. Phytopharm have, however, signed a licensing agreement with Pfizer, who will market P57 in the rest of the world.

Figure 1. *Hoodia* seedlings being propagated in a glasshouse. Figure kindly supplied by Phytopharm (Godmanchester, UK).

The evidence

P57 is advertised as 'an appetite suppressant without the undesirable stimulant effects of conventional treatments'. Dixey says that animal studies, in which they looked at both eating behaviour and general behaviour, have shown that the drug does not have a sedatory effect either. Before patents are secured, Phytopharm are reluctant to disclose the compound's chemical composition or the exact mechanism-of-action. However, Dixey points out that they have put great effort into establishing how the material works. In addition, they have made many semi-synthetic derivatives of the compound. Dixey adds that 'it is quite an unusual molecule in that it is an orally available anorectic agent'. Treatment with P57 produced a significant weight loss and had a good safety profile in a variety of preclinical studies using rats, mice and dogs.

In December 2001, Phytopharm announced the completion of a proof-of-principle study in humans. A total of 60 patients took part in this double-blind, placebo-controlled study. During the first two stages of the study (24 and 16 men, respectively), they assessed the safety, tolerability and pharmacokinetics of ascending single doses and of repeated dosing in healthy overweight volunteers. In the third phase, they moved on to investigate the effects on calorie intake in 19 overweight men who took the compound or placebo twice daily for 15 days. By the end of the study, men in the treatment group achieved a 30% reduction in calorie intake, accompanied by a significant reduction in body fat content by 1 kg. Dixey says, 'This was a very demanding clinical study because people had nothing to do but eat and watch TV. To get an appetite suppressant to work in such an environment was very impressive and it shows how potent this drug is.'

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Box 1. Currently available anti-obesity drugs

Centrally acting appetite suppressants

Phentermine increases the release of noradrenaline. Because of its stimulant action, it has addictive potential and is only recommended for short-term use of less than three months. Although the drug is still available in the USA, it has been withdrawn from European markets because of concerns that its use could lead to valvular heart disease and pulmonary hypertension.

Sibutramine inhibits the re-uptake of serotonin and noradrenaline, thereby prolonging the effect of these appetite-regulating neurotransmitters. It does not seem to have amphetamine-like abuse potential and has been licensed for the long-term treatment of obesity. However, if patients are already being treated with other psychotropic drugs, there are risks of drug interactions and compliance problems.

Drugs inhibiting nutrient and calorie absorption

Orlistat inhibits the pancreatic lipase, which results in decreased fat absorption. The drug can have serious gastrointestinal side effects, such as steatorrhea (excessive fat in the stools), if taken with fatty foods. Because there is insufficient experience with the long-term use of orlistat, the drug is only licensed for use for up to two years.

Future studies

Susan Jebb at the MRC (Medical Research Council) Human Nutrition Research centre in Cambridge, UK, acts as an independent consultant advising Phytopharm on how to design the dietary aspects of their clinical studies. She agrees that the results of the proof-of-principle study are very encouraging. However, she stresses that it is early days. 'The studies they have done so far are only up to two weeks long. Now, they have to do longer studies in more people to demonstrate that this is a consistent effect. Obesity is a chronic relapsing problem and you need a treatment that is going to work safely and effectively over much longer periods of time.'

Dixey says their next step will be to take a closer look at the dosing interval and other pharmacodynamic parameters. 'In parallel with that, we have a large semi-synthetic programme with other active molecules and we are doing a lot of work on the mode of action'. Phytopharm are hoping to have a drug on the market by 2006.

References

1 Froguel, P. and Boutin, P.(2001) Genetics of pathways regulating body weight in the development of obesity in humans. *Exp. Biol. Med.* 226, 991–996

2 Astrup, A. (2001) Healthy lifestyles in Europe: prevention of obesity and type 2 diabetes by diet and physical activity. *Public Health Nutr.* 4, 499–515

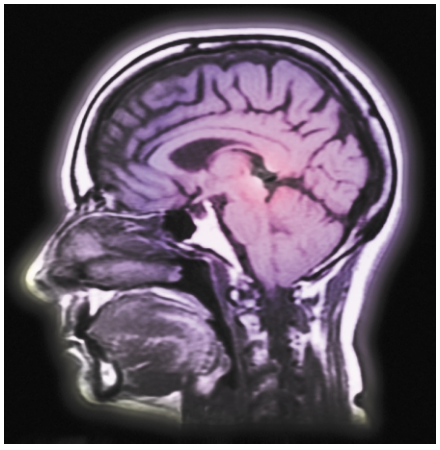
News in brief

CNS disorders

Folic acid deficiency linked to PD

Scientists have found that a deficiency in folic acid could increase the brain's susceptibility to Parkinson's disease (PD)[1]. The study, carried out at the National Institute on Aging (NIA) Gerontology Research Center (Baltimore, MD, USA) provides the first direct evidence that folic acid might have a role in protecting against age-related disease.

Researchers fed one group of mice a diet that included folate, and a second group a folate-deficient diet, followed by moderate amounts of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a chemical that induces PD-like symptoms. The folate-deficient group developed severe PD-like



symptoms in contrast to the group fed with folate, which developed only mild symptoms of PD. Further analysis revealed that the folate-deficient group had elevated levels of plasma homocysteine, an amino acid that exacerbates the effects of MPTP including dopamine depletion, neuronal degeneration and motor dysfunction.

Mark Mattson, Chief of the NIA's Laboratory of Neurosciences, comments: 'It is clear from this study that a deficiency of [folic acid] is associated with increased toxin-induced damage to the dopamine-producing neurons in the mouse brain.' He suggests that consuming folic acid, either though diet or by taking supplements, could be beneficial in the prevention of age-related diseases such as PD.

1 Duan, W. *et al.* (2002) Dietary folate deficiency and elevated homocysteine levels endanger neurons in models of Parkinson's disease. *J. Neurochem.* 80, 101–110

DREAM come true for pain relief

A novel genetic mechanism has been discovered that offers a new approach to pain relief [2]. Scientists at the University of Toronto, The Hospital for Sick Children

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