IN SEARCH OF FAT PROFITS

A pill to prevent obesity is proving as elusive to the drug industry as weight loss is to a growing proportion of the population. **Geoff Watts** assesses the latest candidates

With at least 400 million people worldwide judged to be obese,¹ the hard pressed personal trainer needs an assistant. But not necessarily someone else in shorts and running shoes, badgering overweight people to do five minutes more on the exercise bike. The new help—out of sight, and in a laboratory somewhere—could be a “chemical metabolic engineer.”

Pharmacological attempts to tackle obesity are nothing new. Thyroid hormones have long been known to cause weight loss; unfortunately, that is not all they do. But the molecular biology of metabolic control has moved rapidly during the past decade or so. This is perhaps why Ronald Evans, speaking to the 2007 experimental biology meeting in Washington, DC, at the end of April, felt sufficiently confident about the future to invoke that bold concept of chemical metabolic engineering.

Professor Evans runs the gene expression laboratory at the Salk Institute in La Jolla, California. The genes he studies include a family that code for peroxisome proliferator activated receptors (PPARs). Different members of the PPAR family have different functions. One called PPAR δ , his current preoccupation, seems to act as a master regulator of the body's metabolism. Its activity determines whether the body's cells store fat or burn it.

Professor Evans has shown the role of PPAR δ through genetic manipulation.² He has created mice in which the gene, instead of being switched on when required to regulate the body's fat stores, remains in the “on” position all the time. These modified mice weigh 20-35% less than their normal counterparts eating the same diet. They are also resistant

to high fat diets that would otherwise make them grossly obese.

As Professor Evans commented in his Washington presentation,³ although this genetic metabolic engineering shows the effects of PPAR δ in mice, it's hardly suitable as a remedy for humans. What we need is a chemical method of flipping the switch: a pill that can put the body into fat burning mode whenever circumstances require. Indeed, he seems to have such an agent: “a synthetic chemical designed to mimic fat,” as he described it at the Washington meeting. Whether this compound would be suitable for human use remains to be seen. Either way, if Professor Evans really has identified the metabolic master switch, it should be just a matter of time before this compound, or some other like it, can be devised to manipulate the system.

Complex regulation

That at least is the hope; turning it into reality may not be so easy. Most living things have always had to cope with variable access to food. To keep energy intake in balance with energy output, natural selection has endowed mammals and other higher organisms with a means of storing energy in times of feast and mobilising it in times of famine. But, during the millions of years over which this system evolved, the prevailing condition has usually been shortage rather than surfeit.

As Jeffrey Flier of Beth Israel Deaconess Medical Center in Boston has pointed out,⁴ “Since survival is more acutely threatened by starvation than by obesity, it should come as no surprise that the system is more robustly organised to galvanise in response to deficient energy intake . . . than to excess energy.” To lay down fat rather than dispose of it, in other words. Most people in most developed coun-

tries now have effortless access to unlimited amounts of an unparalleled variety of foods; so the emergence of obesity is hardly to be wondered at. In seeking artificially to throw the metabolic master switch from energy saving to energy burning, scientists are trying to buck the trend of our entire evolutionary history.

Underpinning this hurdle—and in part accounting for the difficulty of crossing it—is the emerging complexity of the systems controlling food intake and energy balance. Each discovery raises new hopes of a remedy: hopes that have thus far turned out to be difficult if not impossible to fulfil. Leptin is a case in point (box). Since then several other signalling molecules have been found, many of them concerned principally with the modulation of appetite. One such hormone is peptide YY, or PYY. Made by cells in the lower part of the gut, it's released in response to food. Experiments by Stephen Bloom of Imperial College have shown PYY to lessen appetite in humans⁷ and reduce their food intake over 24 hours by a third. This finding triggered another small flood of speculative enthusiasm.

Could PYY be therapeutically useful? “In animals it works for at least two or three weeks without any great problems,” says Professor Bloom. “There's no reason to think it won't work in humans, but it just hasn't been administered for any length of time.” There has been interest in giving it through a nasal spray, although Professor Bloom is not convinced that PYY in short bursts would be effective.

He has also been pursuing another gut hormone from the same family: pancreatic polypeptide. In a small preliminary experiment,⁸ he and his colleagues showed that an intravenous infusion blunted the appetite of 10 volunteers, who also ate less of a buffet lunch served two hours later. As with PYY,

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limit appetite and boost energy expenditure. But whatever the chosen means, Professor Bloom thinks this is the right territory to be scouting: “If control is going to succeed, it’ll surely be the manipulation of a natural regulating mechanism that’s got the best chance.”

Maybe that’s why the record so far is not encouraging. Some drugs—fenfluramine, for example—have already been abandoned. But Professor Cawthorne remains confident about the future: “I think it’s only a matter of time because the rewards for the pharmaceutical industry are potentially so great. And there’s also a recognition around the world that obesity is so serious.”

Healthier eating and exercise will remain the first line of attack, he thinks—but by themselves they are not enough. “We’re not going to be able to turn the clock back and return people to agricultural communities where they work the land. It’s unrealistic.”

Given the rate at which knowledge of these control systems is accumulating, trying

to predict the future of obesity management is far from easy. But this didn’t deter Professor Cawthorne from having a go when the Department of Trade and Industry’s foresight programme requested his thoughts on the matter.⁹

He drew attention to rodent experiments¹⁰ showing that adult energy balance can be preprogrammed by administering leptin in utero and in early life. “Might one be able to supplement human milk with leptin?” he wondered aloud in a recent press interview—triggering yet another frenzy of speculation. In fact this idea is not so far removed from attempts to prevent adult obesity by nutritional intervention in early life: a concept already being explored through the European Union funded Early Nutrition Programming Project.¹¹ If dietary change alone doesn’t succeed in doing the trick, here too, there may be a demand for drugs. The pharmaceutical struggle against obesity may yet begin at birth, or even before it.

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sustained exposure to pancreatic peptide seems to be necessary. It might, Professor Bloom cautiously suggests, be incorporated into chewing gum. “These peptides are absorbed across the buccal membrane, and chewing is something that people suffering from excessive hunger quite like doing.”

One pitfall he doesn’t expect is unacceptable side effects. His confidence stems from observations of a type of benign pancreatic tumour that secretes the hormone in abnormal amounts. “These people may have had high levels of pancreatic polypeptide for 10 or 15 years. It doesn’t appear to raise blood pressure or heart rate, or have any other side effects.”

Picking the right path

PPAR δ , PYY, and pancreatic polypeptide are only three of the hormones and receptors currently under scrutiny. Other types of chemical intervention have also been tried. One of the few anti-obesity drugs currently on the market, orlistat, inhibits pancreatic lipase and so interferes with the absorption of fat, although at the price of unpleasant stools and the risk of anal leakage.

In view of the large number of possible points of intervention in the eating and metabolic control systems, it’s far from clear which avenue to follow. And, confusingly, theory isn’t always a reliable predictor of practice. According to Mike Cawthorne of the University of Buckingham: “You can show that a particular target is involved in food intake—but if you then inhibit it, nothing may happen. Another part of the control system has taken over. There’s an incredible amount of redundancy.” This is, of course, what you would expect in so vital a system. The way round this, Professor Cawthorne thinks, may lie in using a combination of drugs to both

LEPTIN: FALSE HOPES

The excitement over leptin began in the mid-1990s with the location of the mouse obesity gene dubbed “ob” and, subsequently, the leptin protein for which it coded.⁵ Strains of leptin deficient mice grew fat; but once leptin had been administered, their obesity vanished. Here, it seemed, was the anti-obesity magic bullet that might work in humans.

It was not to be. Except in a small number of people whose obesity is due to inherited leptin deficiency,⁶ attempts at using it therapeutically have not been effective. Indeed, most fat people turn out not to have less leptin but proportionately more of it: a parallel with insulin resistance in diabetes.

It’s now thought that fat cells produce leptin not so much to prevent the emergence of obesity in times of plenty as to protect against too much weight loss when times are hard. Extra doses of leptin have little effect on metabolism or behaviour.

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