The fat in the fire

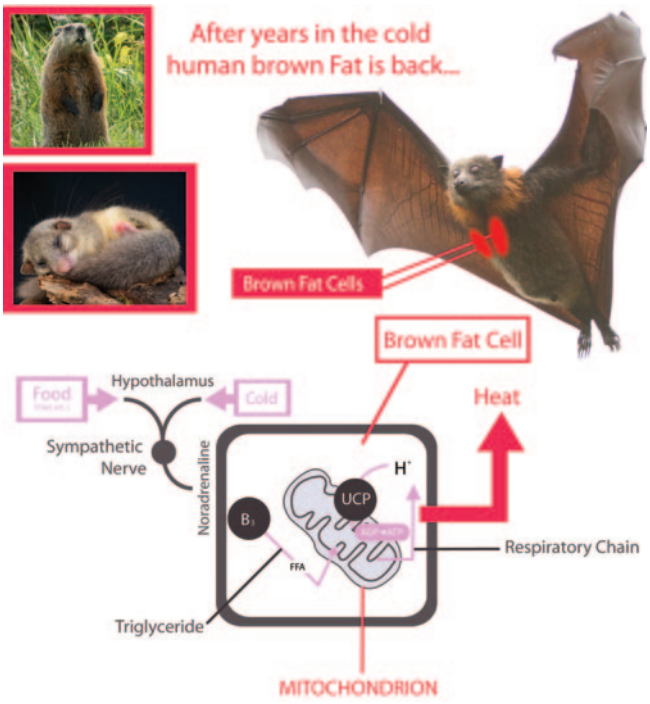
The Buckingham Institute of Translational Medicine speculates on the role of brown fat in fighting metabolic disease

IN 1975 a group of scientists, led by the author, at Beecham Pharmaceuticals decided to search for compounds that would increase energy expenditure as a treatment for obesity. The premise for this approach was that it was clear from the earlier work of the pioneering nutritionist Elsie Widdowson that one could identify pairs of individuals doing similar jobs and eating the same amount of food, but they were of very different body weight and fatness. So there was something in the lean individual that allowed them to dissipate the excess energy. As a result, the Beecham group built an experimental system in which they could measure the energy expenditure of mice over a 24-hour period, and hence seek compounds that would stimulate energy expenditure.

BMI

In the mid-1970s the rate of obesity (BMI >30) was 16% in the US and, whilst lower in Europe, it was beginning to cause concern, such that the UK Department of Health and the Medical Research Council set up a working group to examine the problem. They concluded: "We are unanimous in our belief that obesity is a hazard to health and a detriment to wellbeing. It is common enough to constitute one of the most important medical and public health problems of our time, whether we judge importance by a shorter expectation of life, increased morbidity, or cost to the community in terms of both money and anxiety. It is difficult to document the importance of obesity statistically; it receives only one line in the International Classification of Diseases. This may be compared with 'congenital disorders of lipid metabolism', which receives 22 lines.

Today the rate of obesity in adults in the US is 34% in men and 36% in women. Rates across Europe vary, with the UK towards the top at 24% in men and 26% in women.



The possibility of treatment

The drive to seek agents to stimulate metabolic rate contrasted with drug treatments at that time, which involved short term treatment for no more than 12 weeks, with drugs to suppress appetite and food intake. The 12-week limit was partly because the drugs available were amphetamine-based, but also due to the beliefs that obesity was the result of gluttony and sloth (and so stopping the gluttony should completely reverse the obesity syndrome) and that patients should be able to stay at their reduced weight. This approach contrasted, for example, with the treatment of high blood pressure, where drugs would continue to be taken to maintain the reduced blood pressure within the normal range.

The team at Beecham was able to identify a class of new drugs that stimulated energy expenditure in obese mice and rats. Not only did these drugs slim down the laboratory rodents, they were also highly effective in the treatment of the concomitant Type 2 diabetes. The drugs were believed to act at a β-adrenoceptor. However, at the time the only β-adrenoceptors identified were β1 and β2-adrenoceptors, and these compounds were clearly acting at a different receptor – referred to as atypical but ultimately shown to be a β3-adrenoceptor.

At the same time as this work was proceeding, Michael Stock and Nancy Rothwell (now Dame Nancy) were trying to understand how rats were able to resist weight gain when fed a so-called 'cafeteria diet' composed of typical snacks eaten by Man. Both groups simultaneously realised that the energy dissipation was probably due to the ability of brown adipose tissue (previously known to be present in hibernating animals) to burn metabolic fuels and, instead of generating adenosine triphosphate, give off heat. In Cambridge Philip James and Paul Trayhurn, working with a spontaneous obese mouse as a result of a mutation, also showed that this mouse had virtually inactive brown adipose tissue.

The work of the Beecham team was followed by several pharmaceutical companies, including Lilly, Roche, ICI (now AstraZeneca), Merck and American Cyanamid (now Pfizer).

Unfortunately, none of the compounds developed, although they were very effective in rodents in treating obesity and Type 2 diabetes, were sufficiently efficacious in Man to merit serious clinical development. Why did the compounds fail? The first issue was they were developed in a pre-genomic era without the benefit of cell lines expressing the human genes. The compounds were both less efficacious at the human β3-adrenoceptor than at the rodent receptor, but were also much less selective from β1 (increase in heart rate) and β2-adrenoceptor (muscle tremor) side effects. Indeed, this was probably the first occasion when species differences in the structure of the receptor between rats and mice and Man was sufficient to make the compounds useless as therapeutics.

Brown adipose tissue

The problem of species specificity could be overcome by new chemistry, but from the early 1980s until about 2009, the prevailing view was that brown adipose tissue, although present in human neonates and infants, did not occur in significant amounts in adult Man. This certainly influenced pharmaceutical management to close these research programmes.

Evidence that brown adipose tissue did exist in adult Man came from the cancer biologists. The use of positron emission tomography combined with computed tomography to measure and localise the uptake of 18F-fluorodeoxyglucose into tissues was used to identify tumours. They found high uptake of this tracer into what appeared to be symmetrical tumours running close to the major blood vessels close to the spine. Surgical intervention showed they were not tumours but brown adipose tissue.

These studies have led to a resurgence of interest in brown adipose tissue as a target for thermogenic anti-obesity drugs, and this has been further spurred by the discovery of a lineage of 'beige' or 'brite' fat cells in white adipose tissue deposits. These beige cells develop following exposure to cold, high intensity exercise and by treatment with some drugs, particularly the thiazolidinedione insulin sensitiser agents such as rosiglitazone.

Unfortunately, the amount of functional brown fat in obese subjects is less than in lean, and it also seems to be lost with ageing. Therefore, in considering a treatment it is necessary not only to be able to activate the brown fat (and the beige cells), but also to increase the number of brown fat cells and the overall thermogenic capacity of individuals.

β3-adrenoceptor

If brown adipose tissue plays a significant role in adult humans, should β3-adrenoceptor agonists be reconsidered for the treatment of both obesity and Type 2 diabetes? In rodents, dogs and rhesus monkeys, earlier studies showed that β3-adrenoceptor agonists not only activate thermogenesis but, when given repeatedly, they increase the capacity of brown fat to respond to acute activation. There is no reason to suspect the same would not happen in humans, because the β3-adrenoceptor is certainly present in human brown fat. Moreover, in pheochromocytoma, an adrenal medulla neuroendocrine tumour, over-secretion of noradrenaline and adrenaline (which are the natural agonists for the β3-adrenoceptor) causes a marked increase in brown fat mass, and this is associated with a reduction in the body fat mass.

The β3-adrenoceptor is also expressed in the smooth muscle of the bladder, and a β3-adrenoceptor agonist, mirabegron, has been developed for this disorder which affects some 33 million people in the US. The company marketing mirabegron has clearly decided that overactive bladder treatment is a much safer focus. However, in a recent study it was shown (at a dose four times that used for the bladder indication) to increase metabolic rate by 13% in an acute study. If this level of thermogenesis could be sustained, then one could expect a fat weight loss of 5kg in the first year of treatment.

Will the pharma industry follow-up on this? Despite the huge market and unmet clinical need I suspect not. Why? Obesity is associated with major co-morbidities, including Type 2 diabetes, cardiovascular disease and some cancers. Thus, downstream some patients taking any drug will inevitably develop one of these conditions and class actions will develop in the US, with the lawyers knowing that pharma will pay up rather than face a long battle to defend a potentially innocent drug.

Alternative approaches

Are there other approaches, such as nutraceuticals – substances present in edible plants that will stimulate metabolic rate? Work so far has demonstrated effects by some materials such as capsinoids and oolong tea. However, the benefits of these have proved to be small, and a more comprehensive search is needed to possibly find edible vegetable matter that not only stimulates energy expenditure but also suppresses appetite, since any benefit of an agent that increases energy expenditure just like exercise can be overcome by additional food consumption. The author's laboratory has identified a number of promising agents.

Professor Mike Cawthorne leads the Buckingham Institute of Translational Medicine based at the Clore Laboratory, University of Buckingham, which has research interests in treatments for Type 2 diabetes, obesity and metabolic disease. Its staff members include Jon Arch, Paul Trayhurn and John Clapham, who collectively have the largest and longest experience of brown fat research worldwide.

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