Obesity

Melissa P Ford looks at obesity in relation to diabetes

The current opinion in medicine is that diet is definitely not entirely about willpower. It's controlled mostly by the brain, which gets signals and sends signals to other organs and systems implicated in metabolism. We came to think of dieting as a matter of willpower because for the past 500 years or so of Western medicine we didn't know just how many hormones, enzymes, and neurons are truly implicated in metabolism. But now we are beginning to get our heads around substances and structures within the body that have never been appreciated before.

Even if you crave food because of a nutritional deficiency, ingesting more calories than you expend or metabolize will cause weight gain. We can make a long list of the factors that can contribute to people eating more than they need or exercising less than they ought to (telly, the Internet, junk food, unsafe neighborhoods, lack of pavements in cities, dangerous weather conditions, chronic dehydration, video games, depression, inadequate local sports facilities, driving a car for work, soda consumption, gigantic food portions at restaurants, working at a desk, eating fast food, not having time to cook, not having time to exercise, a sore toe...). And there are some genetic disorders for which obesity is a symptom. But most people who are not candidates to be case studies in textbooks could theoretically lose weight by eating less and moving more. It's calories, calories, calories, all the way down. If one weighs 20 stone, it can be hard to move so exercise may be a toughie at that point, but after bariatric surgery weight loss can be maintained through diet and exercise. The dirty secret of the field of nutrition, is, however, that "energy balance" is a buzzphrase with practically no data behind it. The only way to know if you are eating the right amount of food and doing the right amount of activity is if you are in good shape and your blood test results and vital signs are all right. There are no hard and fast rules, the "food pyramid" is based on some of the worst science around, and genetics are largely responsible for dictating metabolism. We control what we decide to put in our mouths, ultimately, but the signals that ask us to pick up chocolate, coffee, dirt, pickles, ice cream, or a hamburger are very real.

The most promising new pharmacological agents for obesity do not act on the digestive system to interfere with fat storage the way that drugs like Xenical (orlistat) or Meridia (sibutramine) do. They act on the **brain** and the **endocrine system** instead. Sanofi-Aventis's pill Acomplia (rimonabant) has been through a number of clinical trials and would be the first drug in a new class called endocannabinoid receptor blockers if it is approved. The endocannabinoid system is indeed involved in the enjoyment of cannabis, but what's really interesting is that in some people, eating can excite the same region of the brain, creating a veritable addiction to the pleasure that one may experience from eating. Block the endocannabinoid receptor and eating isn't as much fun anymore so you don't **want** to eat; you eat only when the tummy rumbles, etc., and can lose weight. (Side note: at every talk that someone from my company has attended about rimonabant, someone who thinks he's very clever has asked a silly question like, "Did you get the mice to smoke cannabis?" [Berlin] or "So why are there any skinny pot smokers? [Washington, DC])

The other very promising agents for weight loss are injectable substances that work on the endocrine system, for the most part. Symlin (pramlintide), approved in March 2005 by the US FDA for type 1 and type 2 diabetes patients who whose control is okay (7.5-9% A1C) but could be improved by a reduction in postprandial hyperglycemia, is also being trialled as an obesity treatment in non-diabetic subjects. It is a synthetic version of the human hormone amylin that is also knocked out when one develops type 1 diabetes or has beta-cell dysfunction in type 2 diabetes. Type 1s who take Symlin who could stand to lose a few drop an average of 5 to 10 lbs and keep it off as long as they are taking Symlin. But type 1s who are thin already don't lose weight. Because it's not absolutely essential to survival, no one thought it was very important until recently. It was only discovered about 15 years ago but now its potential is huge. Lilly has partnered with Amylin Pharmaceuticals (the company that makes pramlintide) to market Amylin's other current product, a GLP-1 mimetic called Byetta (exenatide), which was approved by the FDA in April 2005.

The awesome thing about exenatide, which has been approved in the US for type 2s who are not doing well on oral medication as a strategy to try *before* prescribing insulin, is that it lowers blood glucose **without causing hypoglycemia** to the same extent that insulin can. It also makes people lose weight! Exenatide is made from gila monster spit (synthesized from a sample in a lab, not harvested from real monsters). It is called a GLP-1 mimetic because it acts just like GLP-1 in humans. GLP-1 is a gut hormone in a class called incretins that are stimulated to a greater extent by oral consumption of carbs than they

are by an IV injection of the same amount of glucose. That means that when you get injected with 50 g glucose, you might have an insulin secretion response that's a 2 on a scale of 5. But if you *drank* 50 g glucose, you would get an insulin secretion rise that's more like a 5 on a scale of 5. (But of course if you have type 1 diabetes you just get a high blood sugar either way because your pancreas can't do anything really.)

GLP-1 helps to increase insulin secretion from the pancreas in a glucose dependent manner (if bg is high, giving GLP-1 will help bring it down; if glucose is low, GLP-1 will not make it drop - but *insulin* makes blood sugar go down even if it's already low because crosstalk with the liver is dysfunctional or nonexistent in diabetes). GLP-1 is deficient in type 2 diabetes, which is implicated in impaired glucose tolerance that leads to hyperglycemia. As I understand it work is ongoing to determine why GLP-1 becomes deficient in type 2 diabetes; at this point it is accepted that GLP-1 is deficient but not clear why.

Exenatide has also been shown to help improve islet health in animal models of diabetes and the US National Institutes of Health are conducting a trial in long-term type 1s to see if it has potential to help cure type 1.

There are other approaches to metabolic manipulation of weight in development - oxyntomodulin (Imperial College London), cortisol synthesis inhibitors (DiObex and Cortendo partnership for one), and more that I can't remember right now!

Author: Melissa P Ford <mford@hotmail.com>. Melissa P Ford is not a medical professional. She has Type 1 diabetes and uses an insulin pump. The information given here is based on her own personal experience. More about Melissa P Ford...

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