Netherlands
The Journal of Medicine

EDITORIAL

Obesity: is evolution to blame?

M.J. Serlie[1], S.E. La Fleur[2], E. Fliers[1]

[1]Department of Endocrinology and Metabolism, [2]Laboratory of Experimental Endocrinology, Academic Medical Center, University of Amsterdam, the Netherlands, e-mail: m.j.serlie@amc.uva.nl

Fighting the obesity epidemic has become an important target for many health programs in industrialised countries, but attempts to maintain persistent clinically significant weight loss by lifestyle interventions, behavioural therapy or medical treatment have not been very successful so far. Current research is mainly focused on unravelling the medical consequences of obesity. It aims to understand how excessive caloric intake and the resulting increased fat mass cause insulin resistance and other features of the metabolic syndrome. However, is studying the consequences of obesity the best choice to control the worldwide obesity problem? Based on our traditional medical thinking founded by Hippocrates, treatment of medical disorders should rely on an understanding of their underlying cause in addition to fighting their consequences. Would more knowledge on the cause of obesity, beyond the concept of excessive caloric intake and reduced energy expenditure, help us to treat our obese patients?

In this issue, Hanno Pijl puts this challenge into a fascinating evolutionary perspective and proposes that we should explore evolution to understand the current obesity epidemic.[1] He explains how a very early climate change enabled us to shift from carbohydrates to fish- and meat-based diets, in turn stimulating encephalisation. The resulting greater cognitive abilities stimulated access to high quality food even further, while seasonal food insecurity spurred the evolution of thrifty genes. The current rapid change in our habitat, driven by technology, exposes most of us to unlimited availability of calories, in particular in the form of refined sugars and saturated fat. Combined with a decreased necessity for physical activity, obesity almost seems a logical consequence. Still, not every adult is obese.

CHANGE IN MACRONUTRIENT INTAKE

Recently our understanding of the way by which the change in macronutrient intake affects body weight has increased significantly. Both in rodents and humans, a diet rich in saturated fat and sucrose (HF/HS) compared with a high fat (HF)- or high sucrose (HS)-only diet, affects appetite control by increasing the drive to eat.[2,3] Moreover, HF/HS has more potent negative effects on glucose metabolism compared with HF or HS alone, irrespective of fat mass.[4] This could be one explanation why the change in the composition of our daily food might promote insulin resistance and obesity. But what could be the underlying mechanism of the effect of an HF/HS diet on food intake and metabolism? The answer to this important question probably lies in our brain. The brain, especially the hypothalamus, is responsible for orchestrating our energy metabolism. Peripheral metabolic signals inform our brain on the actual energy status. The hypothalamus reacts by integrating signals for eating behaviour, anterior pituitary function, as well as the sympathetic and parasympathetic outflow to insulin-sensitive tissues including the pancreas. HF/HS diets induce a state of relative insensitivity to these peripheral signals,[5] resulting in a hungry mediobasal hypothalamus reflected by elevated orexigenic signals, such as neuropeptide Y, a reduced insulin response and insulin resistance. Reducing the insulin response and inducing a state of insulin resistance reduces energy uptake in insulin-sensitive tissues and facilitates energy loss. Is this a way our body tries to get rid of the surplus energy? Perhaps, but then again storage of energy surplus in adipose tissue guarantees survival in times of food shortage. One might speculate that a threshold for optimal weight is present within each person. Trespassing this threshold will inevitably result in attempts to reduce further energy storage and to promote energy loss. From an evolutionary point of view, such weight boundaries make sense because both under- and overweight hamper fertility and mobility, putting us at risk to get caught by predators. Pijl proposes that insulin resistance may serve yet another purpose, i.e., to protect the brain from glucose deprivation. Although this would make sense in a lean fasting individual, insulin resistance in obese subjects is most explicit in the postprandial state when glucose

deprivation is least expected. However, an increase in free fatty acids (FFA) is present in both conditions, possibly reflecting a signal involved in insulin resistance. Despite a possible mechanism on how present-day HF/HS diets interfere with caloric intake and metabolic health, a clear hypothesis on why it is beneficial for survival to promote energy intake in the presence of HF/HS food is lacking at present.

As discussed by Pijl, fat intake has shifted from unsaturated to saturated fat. Is this shift an additional risk for health and body weight homeostasis? Studies in rodents have shown that unsaturated fatty acids, but not saturated fatty acids, have an anorexigenic action by stimulating pro-opiomelanocortin (POMC) gene expression in the hypothalamus.[6] In addition saturated fatty acids have a well-established negative effect on insulin signalling[7] besides a pro-inflammatory potential.[8] Intake of saturated fat in combination with refined sugars (HF/HS) would thus induce a state of excessive caloric intake, insulin resistance and inflammation. It follows that many palatable foods are bad news for metabolic health. Food programs in schools should incorporate this knowledge, e.g., by excluding HF/HS snacks from the assortment.

CHANGE IN ENERGY EXPENDITURE

As pointed out by Pijl, the industrial revolution made our lives much easier as physical fitness was no longer required to guarantee availability of food. Energy expenditure related to physical activity on average accounts for 30 to 50% of our daily energy expenditure. Increasing energy expenditure by performing regular physical activity sports will promote a zero energy balance. Current guidelines advocate 30 minutes of physical activity daily. If a man with a stable weight of 70 kg briskly walks for 30 minutes, seven days a week, his physical activity-induced increase in energy expenditure corresponds to 135 kcal x 7 = 945 kcal/week or 49,140 kcal/year. When he refrains from this daily walk without adjusting his diet by minus 50,000 kcal yearly, he will gain approximately 6 kg every year. This simple example illustrates how much a small change in energy expenditure affects body weight. Still, the question why some subjects do not adjust their caloric intake while reducing energy expenditure remains unanswered and suggests that an unbalanced hypothalamic control of eating behaviour may be a major pathogenetic factor.

GENES

Although a high percentage of adults is overweight and obese, the majority of adults fall within the optimal BMI range. These lean adults, living together with their obese peers in an obesogenic environment, deserve more scientific attention. What protects these adults from becoming obese? Moreover, why do not all obese subjects become diabetic despite the presence of excessive amounts of adipose tissue? Explaining differences between individuals always involves the issue of genetic susceptibility as well as epigenetic factors. As Pijl points out, most genetic variants established in populations with DM2 involve genes encoding for proteins involved in normal β-cell function. While polymorphisms in these genes may explain in part why an obese insulin-resistant subject would become hyperglycaemic, the obese phenotype remains largely unexplained. Monogenetic causes of obesity are present (5 to 7%) in the minority of the obese population.[9] Most of these mutated genes, such as those in the melanocortin 4 receptor, encode for proteins that are expressed in the hypothalamus and involved in appetite control. Genes undoubtedly play an important role in obese persons without these mutations, but until now their exact role and contribution remain unknown. A recent study in 250,000 individuals confirmed 14 known obesity susceptibility loci and identified 18 new ones, but the combined effect on BMI of these loci was only modest and accounted for only 6 to 11% of the genetic variation in BMI.[10] As a consequence, whether the thrifty genes hypothesis can explain the 21st century's prevalence of obesity remains speculative at this stage.

TREATMENT OPTIONS?

The most logical treatment of obesity is to reduce caloric intake and increase energy expenditure. Since abandoning the Western lifestyle is illusive and manipulating appetite control has proven to be extremely difficult, reducing energy intake by a combination of decreasing the physical ability to consume large quantities of food and reducing the uptake of calories seems to be the most promising strategy. Indeed, bariatric surgery has proven to be the sole effective therapy in the long term, especially when restrictive and malabsorptive surgery is applied.[11] Increasing energy expenditure by implementing more physical activity in daily life is another utopistic view on how to treat obesity. Increasing energy expenditure by designing agents which are able to uncouple energy need from energy production theoretically would be an interesting option. Finally, replacement of saturated fat by unsaturated fat by manipulating food (including meat) through genetic techniques or by adding metabolically active compounds might be a fruitful strategy.

In summary, our environment has changed dramatically resulting in the continuous availability of high caloric food as well as a reduction in daily energy expenditure.

For a growing percentage of children and adults, this environment promotes obesity and a metabolically unhealthy state. The reason why we do not adapt to our current environment as would be expected from an evolutionary point of view could be because it changed so fast that our genes couldn't keep up with it. Until we have adapted to our new environment, rigorous and rather crude interventions such as bariatric surgery seem to be the only way of reducing obesity-related morbidity and mortality.

REFERENCES

1. Pijl H. Obesity: evolution of a symptom of affluence. How food has shaped our existence. Neth J Med. 2011; 69:159-66.
2. la Fleur SE, Vanderschuren LJ, Luijendijk MC, Kloeze BM, Tiesjema B, Adan RA. A reciprocal interaction between food-motivated behavior and diet-induced obesity. Int J Obes (Lond). 2007 Aug;31(8):1286-94.
3. Giesen JC, Havermans RC, Douven A, Tekelenburg M, Jansen A. Will work for snack food: the association of BMI and snack reinforcement. Obesity. 2010 May;18(5):966-70.
4. la Fleur SE, Luijendijk MC, van Rozen AJ, Kalsbeek A, Adan RA. A free-choice high-fat high-sugar diet induces glucose intolerance and insulin unresponsiveness to a glucose load not explained by obesity. Int J Obes (Lond). In press 2011.
5. la Fleur SE, van Rozen AJ, Luijendijk MC, Groeneweg F, Adan RA. A free-choice high-fat high-sugar diet induces changes in arcuate neuropeptide expression that support hyperphagia. Int J Obes (Lond). 2010 Mar;34(3):537-46.
6. Schwinkendorf DR, Tsatsos NG, Gosnell BA, Mashek DG. Effects of central administration of distinct fatty acids on hypothalamic neuropeptide expression and energy metabolism. Int J Obes (Lond). 2010 Aug 17.
7. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 2000 Jul;106(2):171-6.
8. Iyer A, Fairlie DP, Prins JB, Hammock BD, Brown L. Inflammatory lipid mediators in adipocyte function and obesity. Nat Rev Endocrinol. 2010 Feb;6(2):71-82.
9. O'Rahilly S, Farooqi IS. Human obesity as a heritable disorder of the central control of energy balance. Int J Obes (Lond). 2008 Dec;32(7):S55-61.
10. Speliotes F. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010;42:937-48.
11. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Swedish Obese Subjects Study. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007 Aug 23;357(8):741-52.