



Refined carbohydrates, phenotypic plasticity and the obesity epidemic

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ABSTRACT

The major change in the United States and European diets associated with the increased rates of obesity was an increased consumption of refined carbohydrates. A feature of refined carbohydrates is their predisposition to cause increased fluctuations in plasma insulin and glucose levels and postprandial reactive hypoglycaemia. As the central nervous system is dependent on a stable supply of glucose this threatens the central nervous system functioning and these fluctuations also have a negative impact on the cardiovascular system.

Phenotypic plasticity enables organisms to use adaptive phenotypes already in existence such as the increased insulin resistance and increased adiposity associated with pregnancy or the insulin resistance associated with infection, trauma and burns or to evolve new phenotypes to adapt to variations in the environment.

This paper explores the evidence that increased insulin resistance that is commonly associated with increased adiposity possibly because of shared locations on the genome is a phenotypic plastic adaptation to the increased consumption of refined carbohydrates and their predisposition to cause increased fluctuations in plasma insulin and plasma glucose and post-prandial reactive hypoglycaemia both of which have negative impacts on the metabolism.

Obesity, that is a relatively stable state of increased adiposity and insulin resistance has adaptive and defensive features to these fluctuations in plasma insulin and glucose in that metabolic disorders associated with refined carbohydrate consumption are often mitigated and modified as exemplified by the obesity paradox.

Introduction: the obesity epidemic

The incidence of obesity has increased in all countries over the past 50 years. Two billion people worldwide are overweight and 600 million are obese. In the United States, the incidence of obesity in adults has increased from 11% in 1960 to 40% in 2018, and in young people, the incidence of obesity has increased from 4% in 1963 to about 20% in 2018.

Obesity is an increasing cost to the health care system. In the United States in 1998, it accounted for 6.5% of total health care costs. By 2006 it had risen to 9.1% and by 2012, just six years later, it was 21%.

Type 2 diabetes is a major consequence of obesity. The percentage of United States adults with type 2 diabetes increased from 1% in 1966 to 11% in 2018.

However, the most explosive situation is in China, followed by India. In China, the incidence of type 2 diabetes in 1980 was 1%. In 2013, it was 11%. The incidence of prediabetes increased from 15% in 2008 to 36% in 2013. According to the World Health Organisation, almost half of all adults in China, close to 500 million people, have prediabetes. Moreover, the report states that half of the people in China with diabetes may be undiagnosed, and only 25% with diabetes in 2010 were receiving treatment for their condition.

The ENIGMA

It should be simple for an obese person to reduce to an ideal weight.

A small reduction in calorie intake and/or increased regular exercise over time should be all that is required.

However, the reality is quite different. All studies draw the same conclusion. Diets do lead to short-term weight loss—about an average of 5–10% of weight, but these losses are not maintained. The longer the follow-up, the greater the weight gain. Moreover, 83% of patients followed up for two or more years had not only gained the weight they had lost but had gained even more weight [1].

Other data shows that the failure rate of the obese who try to lose weight and reduce to an ideal weight is 99%, and the majority of that 1% who do succeed will eventually regain that weight loss.

Now this is not for want of trying. In the United States at any one time, 100 million people are on a diet; that is 30% of the entire population. That number comes from the U.S. Weight Loss and Diet-Control Market that merely measures people actively spending money on diet-related products and services. It does not count all the people trying to eat less or get healthier on their own.

The average dieter spends a lot of money and makes five new attempts every year with almost no hope of success.

The treatment for obesity and even the prevention of obesity in children is even less successful. One study compared 300 children in an intervention group with 300 in a control group. These non-obese children were at high risk of becoming obese because of socio-economic factors. However, by 36 months, both groups of children had developed a 35% incidence of obesity, and the trajectories of their weight gains over the 36 months were identical [2].

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Another reason for the obesity epidemic could be reduced physical activity associated with modern life, but this is not supported by objective evidence. Doubly-labelled water studies (which provide the optimal method to measure energy expenditure in free-living individuals) show that daily energy expenditure has not declined between 1980 and 2005 in Europe or North America. Similarly, doubly labelled water studies indicated that populations in industrialised countries do not have lower rates of daily energy expenditure compared with populations in developing countries [3].

However, long-term studies comparing very active and inactive individuals have demonstrated differences in weight gain.

In one study, about 3500 young adults were followed up for 20 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study. In men, the difference in weight gain between the very active and inactive individuals after 20 years was 2.6 kg; in women, it was 6 kg. Nevertheless, very active participants still gained weight over this time, men about 7.5 kg and women about 8 kg. Thus, a high level of physical activity did not completely prevent weight gain. It reduced it by about 25% in men and 40% in women [4].

The embedding of an intermittent phenotype

A definition of phenotypic plasticity is “a capacity of a single genotype to exhibit a range of phenotypes in response to variation in the environment” [5].

The incidence of obesity increases in communities when they replace traditional diets with modern processed foods and beverages. The major dietary change associated with the increased incidence of obesity in the United States and Western Europe over the past 50 years has been the increased consumption of refined carbohydrates [6]. This represents a variation in the environment.

Obesity is highly resistant to change. It is also highly heritable.

Resistance to change and heritability are characteristics of a trans-generational phenotype; this indicates that the increasing consumption of refined carbohydrates is embedding an existing intermittent phenotype such as the one that occurs during pregnancy or during the increased metabolic demands associated with injury, infection or burns. This phenotype initiates insulin resistance to divert plasma glucose resources to the central nervous system when demand threatens to exceed supply.

Increased adiposity and increased insulin resistance commonly co-exist, possibly because of shared locations on the genome.

Diet plays a role in phenotypic expression in other species and can result in epigenetic modifications and/or the use of phenotypes with distinct morphological and physiological differences [5]. The classic example is the honeybee (*Apis mellifera*). The diet fed to their larvae determines those that become queen bees and those that become worker bees. They have identical genes but differ in the methylation of those genes.

The most spectacular example of diet changing the expression of a gene and exposing a different phenotype is the Agouti mouse. This mouse has an abnormal Agouti gene and it is yellow and obese and prone to diabetes and cancer. When these pregnant mice are fed a methyl-rich diet, such as one supplemented with choline, folic acid, betaine and vitamin B12, most of their pups are brown, lean and stay healthy for life.

However, changes in diet are just one of numerous environmental changes that can result in epigenetic changes or the usage of available adaptive phenotypes. An epic bout of cold weather in Texas in the winter of 2014 resulted in a new lizard phenotype. Prior to this event, these lizards were only able to function in a warm climate. After the event, they could function in colder climates characteristic of more northern locations. The adaptation appears to be both plastic and genetic. Other lizards display plasticity in their hind limb length in response to whether their habitat is on flat terrain or on the branches of trees—perhaps the equivalent of tennis players whose serving arms are

longer than their non-serving arms.

Monozygotic twins illustrate the impact of the environment on the epigenome. Although monozygotic twins are epigenetically indistinguishable during the early years of life, older twins exhibit differences, particularly those who had spent less time together, had different lifestyles or who had differing medical histories. Some of these differences in epigenetic changes are thought to be environmentally induced and a factor explaining that the concordance rate in monozygotic twins for psychological disorders is only about 50% and for medical disorders is only about 20%.

Some plastic changes are adaptive, such as immune responses, and some are non-adaptive, such as the type 2 diabetes associated with obesity. Other plastic changes have both adaptive and non-adaptive manifestations. The high incidence of metabolic disorders associated with obesity is clearly a non-adaptive manifestation.

However, the obesity epidemic may also represent an attempt to adapt positively to the increased consumption of refined carbohydrates with manifestations that are arguably positive outcomes: the obesity paradox.

Post-prandial reactive hypoglycaemia

The most pervasive of the refined carbohydrates are sweet sugars. These enhance the palatability of fats and fat/sugar mixtures are the basis of many highly palatable confectionary items. These items are often the focus of intense food preferences and food cravings that are reputed to affect most obese individuals, particularly after they lose weight [7]. Thus, sweet sugars are a key player in the pathogenesis of obesity.

Reactive hypoglycaemia is disruptive metabolically and biologically and seems a likely explanation for why obesity is highly resistant to change and highly heritable. When individuals consume refined carbohydrates, the rapid absorption of glucose causes an exaggerated spike in plasma glucose levels, and this in turn causes an exaggerated spike in plasma insulin levels that is followed by a reactive plunge of the plasma glucose level below normal [8].

Thus, when their glucose levels were monitored while subjects consumed meals with a fixed carbohydrate content (50 g), a meal consisting almost exclusively of refined carbohydrate (toast, honey, jam, curd cheese, orange juice; total 252 calories) resulted in plasma glucose rising as high as 180 mg/dl and falling as low as 40 mg/dl. Another meal, also with 50 g of carbohydrate (kidney beans, wholemeal bread, salami, cheese; total 750 calories), resulted in plasma glucose rising only as high as 120 mg/dl and falling only as low as 60 mg/dl [9].

Thus, reactive hypoglycaemia occurs when refined carbohydrates are consumed without fibre, protein or fat, whereas insulin resistance counteracts hypoglycaemia [10].

The central nervous system and plasma glucose

The human brain's almost complete reliance on a continuous stable supply of plasma glucose points to why insulin resistance is an adaptive response; the brain is quickly damaged by even a temporary disruption in energy supply [11], and although it represents only 2% of body mass in adulthood, it accounts for 20% of the resting metabolic rate (RMR). The brain cannot synthesise glucose or store glucose as glycogen for more than a few minutes' supply, and neuronal tissues are costly because they must be maintained in a state far from thermodynamic equilibrium, which requires a constant redistribution of ions across the cell membrane by using energy-dependant pumps [11].

Thus, a fall in plasma glucose causes an immediate cascade of responses to reverse this fall. These include the induction of insulin resistance to reduce peripheral glucose uptake, particularly by skeletal muscle [8].

However, the glucose requirements of the brain are greatest in childhood and peak at 160 g per day at the age of five years. This is

double the daily glucose use by the brain in adulthood and an average gram of brain tissue at the age of four years uses 2.5 times as much glucose as a gram of brain tissue at birth uses. This reflects developmental dynamics in substrate-intensive processes related to neural plasticity and learning [11]. Thus, it is pertinent to note that rates of obesity in children exposed to the high availability of refined carbohydrates has increased six-fold over the past 50 years compared to the three-fold increase in adult obesity in the United States.

Ketones and the neonate's central nervous system

In addition, human babies are born with more body fat than all other mammals, including seals [12]. In infants, this fat can be converted into ketones in a few hours. Ketones are small water-soluble molecules manufactured from free fatty acids that, like glucose, can cross the blood-brain barrier and be used by the central nervous system as a fuel [13]. By contrast, it takes days for adults to achieve similar serum ketone levels [12]. This adaptation is because glucose supply and requirements are finely balanced in the newborn, so a backup fuel is essential [13]. This is an additional example of the mechanisms evolved to protect the fuel supply for the central nervous system from even the most temporary interruption.

Insulin resistance protects the central nervous system

There are other situations when insulin resistance occurs to protect plasma glucose resources for the central nervous system and directs peripheral tissues to use alternative fuels such as free fatty acids.

Pregnancy is one, and the growing foetus uses glucose and competes with maternal tissues for this resource [14]. The insulin resistance that occurs ensures that the foetus and the mother's brain have priority and peripheral maternal tissues are directed to use alternative fuels such as free fatty acids.

Increased parity is associated with an increased incidence of obesity. This indicates that repeats of the stimulus (pregnancy) to this transient phenotype of increased insulin resistance and increased adiposity increases the likelihood of the phenotype becoming embedded (obesity).

Other states associated with increased metabolic demands, such as infection, injury, burns and shock, are also associated with insulin resistance and this also ensures that the brain has priority access to plasma glucose [15].

Consistent with this model, medications, particularly insulin, which are likely to cause hypoglycaemia, are also likely to result in weight gain (and increased insulin resistance) [16], thus lessening the likelihood of hypoglycaemia. Conversely, acarbose, which minimises the probability of reactive hypoglycaemia by inhibiting the rapid digestion and absorption of carbohydrates, induces weight loss [17].

As with the example of multiple pregnancies increasing the incidence of obesity, recurrent consumption of refined carbohydrates also increases the incidence of obesity, again by embedding the episodic phenotype of increased insulin resistance and increased adiposity.

The negative impact of fluctuations in plasma glucose

Although hypoglycaemia is negative for the central nervous system, fluctuations in plasma glucose are damaging to the cardiovascular system [18,19,20].

Even fluctuations in plasma glucose levels associated with decreased meal frequency are associated with the prevalence of subclinical atherosclerosis [21], and a comparison of a nibbling diet of 17 snacks per day to a diet of three meals per day achieved significant reductions in serum cholesterol, serum insulin and 24-h urinary cortisol excretion [22].

Acarbose, which prevents rapid fluctuations of plasma glucose by inhibiting the rapid digestion of carbohydrate and therefore the rate of

rise in blood glucose and insulin after a meal, achieves comparable outcomes. In one study over three years, it achieved a 49% reduction in cardiovascular events [23]. A meta-analysis of seven long-term studies found that acarbose treatment was associated with a reduction in myocardial infarction by 64%, a reduction in stroke by 25% and a reduction in cardiovascular death by 38% [24].

The paradox

Despite the high incidence of metabolic disorders associated with obesity, some studies, but not all, indicate that obesity appears to bestow a health benefit. This is known as the obesity paradox.

A review of numerous studies concluded that although obesity increases the incidence of many cardiovascular diseases, the overweight and the obese with these diseases have a better prognosis and lower mortality than those of normal weight [25].

For example, a study of 1487 patients with heart failure, of whom 35% were overweight and 47% were obese and who were followed up for 10 years, found that those who were overweight or obese had a 30% lower risk of death [26].

A Canadian study of 44,663 patients who underwent cardiac catheterisation for suspected coronary artery disease (CAD) found that not only did the obese with CAD have a 30% lower mortality rate over the next four years, but even the 10,974 obese patients with normal coronary arteries had a 30% lower mortality rate [27].

A Chinese study produced even more startling findings. It analysed in-hospital mortality among 35,964 patients hospitalised with acute myocardial infarction. Although the obese patients were more likely to smoke and have hypertension, hyperlipidaemia and diabetes, their risk of death was about 35% lower than those of normal weight and about 60% lower than those underweight [28].

The risk of dementia is lower in the obese and inversely related to body weight, with the obese (BMI 30 to > 40 kg/m²) having a 30% lower risk than those of normal weight and a 50% lower risk than those underweight [29].

The risk of death from cardiovascular disease in type 1 diabetics is lower in the obese. Patients with type 1 diabetes were followed up for 20 years. Mortality over years 11–20 was lowest by 50% in the 30% who gained the most weight during years 1–10 [30].

Obese patients with sepsis not only have a lower risk of death but when these patients also have diabetes, the risk was even lower by 50% [31].

An analysis of suicides in the United States found that the obese were about 40% less likely to die from suicide despite having higher rates of gun ownership (the commonest means of suicide) and smoking and lower rates of college education and median household income [32].

Because the obese have higher average plasma glucose levels because of insulin resistance, hypoglycaemia and lower-level fluctuations in plasma glucose and their negative impacts on the metabolism are less likely. This is possibly one explanation for the obesity paradox.

Consistent with this hypothesis, the PROactive study that followed up 5202 subjects with type 2 diabetes and cardiovascular disease over three years found not only the lowest mortality among the obese but also increased mortality in those who lost weight. Loss of 1% of body weight was associated with all-cause mortality (hazard ratio [HR] 1.13) and loss of > 7.5% of body weight was associated with greater all-cause mortality (HR 4.42). Weight gain did not increase mortality. Although weight loss is often associated with malignancy, only 3.8% of subjects developed malignancy and their exclusion did not affect the relationship between weight loss and mortality [33].

Also consistent with this hypothesis, a four-hour oral glucose tolerance test on non-diabetic subjects with coronary artery disease found that asymptomatic reactive hypoglycaemia (mean nadir 64 [59.00–66.0] mg/dl) during the final two hours of the test was common, and this was associated with increased levels of markers of an

increased inflammatory response and markers of arteriosclerosis [34].

Conclusion

Consumption of refined carbohydrates results in increased fluctuations of plasma glucose and plasma insulin and hypoglycaemia. These fluctuations have a negative impact on the central nervous system and the cardiovascular system: metabolic disorders.

Consumption of refined carbohydrates also results in increased adiposity and insulin resistance: obesity.

However, the obese state appears in many studies to be protective or to minimise further damage to the central nervous system and cardiovascular system [33]: the obesity paradox.

Thus, some aspects of obesity are an adaptive and defensive response to this dietary change and thus fulfil the definition of an adaptive phenotypic plastic response.

Taxing sugar-sweetened beverages and restricting advertising of junk foods and beverages to children are being adopted in many countries and are considered important first steps to counteract the obesity epidemic.

A recent rat study suggests that future generations exposed to this obesogenic nutritional environment may have a lower risk from obesity-related metabolic disorders due to epigenetic adaptations. The third generation of rats on the same constant obesogenic diet as the first and second generations had reduced body fat to lean tissue ratios [35].

This may explain the apparently higher rates of obesity and associated metabolic disorders in developing nations compared to older established societies.

However, the current epidemic will only be curtailed by regulation and taxation of the food environment, because possible beneficial epigenetic changes will take more than one generation to become manifest.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.109317>.

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