Overview of the thrifty genotype hypothesis

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The thrifty genotype hypothesis was proposed by Neel in 1962 to explain the increasing incidence of diabetes in the western world. Since then it has been invoked frequently to explain the epidemics of obesity and non-insulin dependent diabetes (NIDDM) in populations all over the world as they have made the rapid transition to a westernised lifestyle in the twentieth century. An examination of the archaeological record indicates that human populations were exposed to nutritional stresses throughout history (both as hunter-gatherers and agriculturalists) which could have selected strongly for a "thrifty" metabolism. The metabolic basis of the "thrifty" genotype has been attributed to selective insulin resistance, in which the gluco-regulatory pathways of insulin action are affected primarily, thereby promoting compensatory hyperinsulinaemia and overstimulation of those pathways less affected by insulin resistance such as those involved in fat deposition. Both physical inactivity and an energy-dense diet high in saturated fat and fibre-depleted carbohydrate have been shown to increase insulin resistance. Thus, key components of the western lifestyle act to exacerbate insulin resistance and facilitate weight gain, which itself also worsens insulin resistance. Finally, Hales and Barker have argued provocatively for a "thrifty" phenotype as the major predisposing factor in NIDDM: that poor nutrition in the perinatal period is associated with increased risk of NIDDM in adulthood, mediated either through sustained effects on β-cell function or insulin sensitivity. The difficulties in differentiating between "nature" and "nurture" in the aetiology of this complex condition cannot be overstated.

Introduction

In 1962, the American population geneticist, JV Neel, put forward a novel hypothesis to explain why the incidence of diabetes was increasing in the western world[1]. He proposed that individuals predisposed to diabetes possessed a "thrifty" genotype which would have favoured survival under the "feast-and-famine" conditions prevailing through much of human history by facilitating efficient fat deposition in times of food abundance and providing an energy buffer for times of food scarcity. He suggested that this efficient fat storage was mediated by a high insulin response - a "quick insulin trigger". However, under conditions of an abundant and rich food supply (and physical inactivity) prevailing in affluent societies in the 20th century, such a "thrifty" genotype is no longer advantageous and predisposes to both obesity and diabetes.

Neel updated and refined his hypothesis in 1982 in the light of emerging knowledge, so that it applied specifically to non-insulin dependent diabetes mellitus (NIDDM). He considered not only his original hypothesis implicating hyperinsulinaemia, but also the possibility that insulin resistance could be the primary defect, or even that there could be a form of selective insulin resistance which was "lipolysis sparing" and thus able to promote efficient fat accumulation[2].

Neel's hypothesis has subsequently been invoked to explain the epidemics of obesity, diabetes and related conditions which have occurred in many populations around the world as they have made the rapid transition from a traditional (agriculturalist or hunter-gatherer) to a westernised lifestyle in the twentieth century[3-8].

Food shortages throughout human history

An examination of the histories of many of the populations now experiencing epidemics of obesity and NIDDM reveals a range of severe nutritional stresses to which they were exposed in their pasts which could have selected strongly for a "thrifty" metabolism[9]. For example, Wendorf and Goldfine have speculated that for the American Indians, such selection may have occurred when their Paleo-Indian hunter-gatherer ancestors were adapting to their new environment in North America, having crossed from Europe during the ice age about 20,000 years ago[10]. Similarly, Zimmet and co-workers have speculated that the ancestors of the Pacific Island populations now experiencing very high prevalences of obesity and diabetes were probably exposed to the cycle of feast and famine through their long canoe voyages and as a result of droughts and hurricanes which would have affected food productivity on their islands[11].

Food shortages were not confined to hunter-gatherers. Indeed, they may have been even more significant after the advent of agriculture[9]. Archaeological evidence of a shorter stature and other skeletal evidence of nutritional stress are consistent with severe and regular food shortages in agricultural societies.

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Metabolic basis of the "thrifty" genotype

In attempting to explain the metabolic basis of the putative "thrifty" genotype, the concept of selective insulin resistance has been invoked by several investigators. Neel speculated in 1982 that the insulin sensitivity of gluco-regulatory pathways may be diminished relative to the lipid metabolic pathways, resulting in compensatory hyper-insulinaemia and overstimulation of those pathways involved in fat deposition[2].

In seeking to explain the particular propensity of Australian Aborigines to obesity and NIDDM when they westernise, we have postulated that selective insulin resistance in the liver (gluconeogenesis insensitive to insulin suppression, lipogenesis normally insulin sensitive) would have maximised an individual's capacity to convert high protein feasts (from lean game) efficiently into readily available energy (glucose, lipid) for metabolism or storage[8]. This would have provided a survival advantage under the feast-and-famine conditions of the hunter-gatherer lifestyle.

Wendorf and Goldfine[10] have suggested that the primary site for insulin resistance is skeletal muscle and that this would have minimised the hypoglycaemia associated with fasting. They also proposed that this insulin resistance affected gluco-regulatory pathways primarily, and thereby promoted compensatory hyperinsulinaemia and overstimulation of those insulin sensitive pathways not subject to insulin resistance such as those involved in fat deposition.

The western diet and lifestyle amplify the "thrifty" genotype

Two qualities of the western diet which distinguish it most strikingly from other diets consumed by humans throughout history and prehistory are its high contents of saturated fat and fibre-depleted (refined) carbohydrates. This energy-dense diet is continuously available and there is strong evidence that it can produce insulin resistance and facilitate weight gain which, of itself, also exacerbates insulin resistance. Likewise, physical inactivity has also been shown to increase insulin resistance in skeletal muscle. Thus, both the western diet and sedentary lifestyle could interact with pre-existing insulin resistance to amplify it and thereby increase the risk of NIDDM.[12] The behavioural traits which were so central to successful survival as hunter-gatherers (the strong preference for energy-dense foods, the capacity to gorge, and the desire to minimise unnecessary physical activity) in combination with the "thrifty" metabolism described above, produce a vicious cycle of weight gain and worsening insulin resistance culminating in obesity, and in those individuals with the additional susceptibility to pancreatic b-cell decompensation, NIDDM.

Nature or nurture - thrifty genotype or thrifty phenotype?

Hales and Barker[13] recently questioned the concept of a thrifty genotype - arguing instead that poor nutrition in utero and early infancy is associated with increased risk of NIDDM, possibly mediated via impaired development of pancreatic β-cells and rendering them susceptible to early failure. In subsequent research from this group[14], the focus has shifted from impaired β-cell function to insulin resistance being the underlying risk factor. They argue that the insulin resistance is acquired as a result of nutritional stresses in early life.

Such a thrifty phenotype hypothesis is not necessarily inconsistent with the thrifty genotype scenario proposed above - indeed it would amplify it. It would also explain the apparent paradox of the co-existence of high rates of infant malnutrition (low birthweight, "failure to thrive") and obesity, NIDDM and coronary heart disease in adults in populations, such as the Australian Aborigines, making a rapid transition to western lifestyle in the 20th century. Without any strong candidate NIDDM genes emerging from intense research, the difficulties of differentiating between nature and nurture cannot be overstated.

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