Insulin resistance and low metabolic rate: do they cause obesity?

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Insulin resistance and obesity have genetic determinants which are separate and probably polygenic. Under certain environmental conditions, both probably offer selective advantages for survival. Under modern environmental conditions, a genetic predisposition to both would result in marked insulin resistance and be a major risk for the development of NIDDM. A low relative metabolic rate and a high insulin sensitivity have been shown to predict weight gain. However, upon the weight gain these "metabolic risks" appear to normalise thus raising doubts about whether these factors are truly aetiological. The thrifty genotype hypothesis remains a valid construct to explain the presence of common, genetically-determined factors which are currently detrimental to health, however, the original mechanisms proposed by Neel of an "efficient" metabolism or hyperinsulinaemia need considerable rethinking in light of 30 years of evidence.

Introduction

Among the major predictors for the development of non-insulin dependent diabetes mellitus (NIDDM) are race, family history, obesity, and insulin resistance[1]. Race and, to some extent, family history reflect the genetic basis for NIDDM. Part of this genetic transmission may be through the genetic determinants of obesity[2,3] and insulin resistance[4]. How is the triad of NIDDM, obesity, and insulin resistance linked and how do these relationships bring us closer to understanding reasons for a high frequency of a NIDDM genotype in populations? Also, is the NIDDM or obesity genotype due to a "thrifty" or "efficient" metabolism as Neel originally suggested?

Relationship between obesity, insulin resistance, and NIDDM

In cross-sectional studies, obesity is associated with insulin resistance, although the relationship is not as tight as commonly believed (r values of about 0.3-0.4) with a considerable spread at all levels of body fatness[5]. From weight gain and weight loss studies, it is well recognised that weight gain cause increases insulin resistance and weight loss decreases it[6].

NIDDM, especially in non-European races, is almost invariably associated with both insulin resistance and obesity[1]. Could insulin resistance, therefore, be the common denominator causing both obesity and NIDDM? If this were the case, the genetic determinants of insulin resistance could be the "thrifty" genotype.

Insulin resistance attenuates weight gain

Three longitudinal studies have shown that insulin resistance attenuates, rather than accelerates, weight gain. The first study in Pima Indians measured insulin action directly using the hyperinsulinaemic, euglycaemic clamp technique and showed that the cumulative incidence of gaining 10 kg of body weight was 3.8 (95% CI 1.7-8.6) times greater in insulin sensitive subjects (90th percentile of insulin action) than in insulin resistant subjects (10th percentile of insulin action). Two further studies, both in Hispanics and Caucasians, confirmed these findings by showing that low fasting insulin levels predicted weight gain[7,8]. Therefore, insulin resistance is unlikely to be the common precursor genotype which explains both NIDDM and obesity.

Selective advantages of insulin resistance

Insulin resistance is common, it appears to be partly genetically determined, and it is implicated in the development of NIDDM, hypertension, dyslipidaemia and atherosclerosis. One could then ask Neel's question: Was there once a selective advantage for insulin resistance? The answer to that must be "yes" if one looks at the physiological role of insulin resistance. Puberty is a period of marked insulin resistance[9] which appears to be related to the growth factor role of insulin. Normal pregnancy is associated with a fall in insulin sensitivity to about 30-50% of the non-pregnant state[10] resulting in a re-direction of glucose away from maternal skeletal muscle and towards the fetus which would be advantageous for fetal growth (unless there was too much glucose as in gestational diabetes). Insulin resistance also develops during starvation and major trauma and sepsis[11], and this serves to re-allocate the fuel supplies of glucose, fatty acids and protein during these stresses. There are undoubtedly a variety of mechanisms by which insulin

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resistance is produced under these conditions (for example, starvation is hypoinsulinaemic and pregnancy is hyperinsulinaemic).

Obesity: Metabolic rate and other predictors of weight gain

Metabolic rate is usually conceptualised as total calories burned in 24 hours in the same way that calorie intake is characterised as total calories per 24 hours. Under these absolute terms, obesity is clearly associated with high metabolic rates (and high energy intake). Researchers in the energy metabolism field, however, usually adjust the metabolic rate to body size (eg kcal/kg fat-free mass/24 hours). This is a different concept. It means that a person can be described as having a high or low metabolic rate relative to what one would predict given the person's body size (mainly fat-free mass).

No population with a high prevalence of obesity or NIDDM has been shown to have lower metabolic rates (absolute or relative) compared to Caucasians. What has been shown is that individuals with a low relative metabolic rate have a higher rate of weight gain than those with a metabolic rate greater than predicted[12]. However, upon gaining that weight, the "abnormally low" relative metabolic rate appears to self correct. This has been seen in other metabolic predictors of weight gain, suggesting that these factors are better viewed as modulators of weight change (preventing large swings in weight) than as causes of obesity[13]. Metabolic predictors of weight gain identified among Pima Indians include a low relative metabolic rate, low ratio of fat: carbohydrate oxidation, high insulin sensitivity, low "fidgeting" activity, low core temperature, and a reduced insulin secretion[14].

The differences in prevalence of obesity between populations are probably explained by environmental differences (such as the national diet) and not metabolic differences. Indeed, the search for a metabolic cause of obesity in certain populations has largely been fruitless. However, within a particular environment, the genetic makeup of some individuals means that they will gain more weight than others. A degree of relative energy "efficiency" or "thriftiness" may explain some of these individual differences in response to a modern environment, but there are likely to be many metabolic determinants of energy or fat balance which also may contribute.

References

1. Knowler WC, Pettitt DJ, Saad MF, Bennett PH. Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. Diabetes Metab Rev 1990; 6:1-27.
2. Stunkard AJ, Sorensen TIA, Hanis C, et al. An adoption study of human obesity. N Engl J Med 1986; 314: 193-198.
3. Bouchard C, Tremblay A, Despres JP, et al. The response to long term overfeeding in identical twins. N Engl J Med 1990; 322:1477-1482.
4. Lillioja S, Mott D, Zawadzski J, et al. *In vivo* insulin action is familial characteristic in non-diabetic Pima Indians. Diabetes 1987; 36:1329-1395.
5. Swinburn BA, Nyomba BL, Saad MF, et al. Insulin resistance associated with lower rates of weight gain in Pima Indians. J Clin Invest 1991; 88:168-173.
6. Sims EAH. Experimental obesity, dietary induced thermogenesis and their clinical implications. In: Albring MJ, ed. Clinics in Endocrinology and metabolism. Philadelphia. WB Saunders, 1976: 377-395.
7. Valdez R, Mitchell BD, Haffner SM, et al. Predictors of weight change in a bi-ethnic population. The San Antonio Heart Study. Int J Obes 1994; 18: 85-91.
8. Hoag S, Marshall JA, Jones RH, Hamman RF. High fasting insulin levels associated with lower rates of weight gain in persons with normal glucose tolerance: The San Luis Valley Diabetes Study. Int J Obes. 1995; 19: 175-180.
9. Savage MO, Smith CP, Dunger DB, Gale EA, Holly JM, Preece MA. Insulin and growth factors adaptation to normal puberty. Horm Res 1992; 37(suppl 3):70-73.
10. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. Am J Obstet Gynecol 1990; 162:1008-1014.
11. Zenni GC, McLane MP, Law WR, Raymond RM. Hepatic insulin resistance during chronic hyperdynamic sepsis. Circ Shock 1992; 37:198-208.
12. Ravussin E, Lillioja S, Knowler WC, et al. Reduced rate of energy expenditure as a risk factor for body weight gain. N Engl J Med 1988; 318:467-472.
13. Ravussin E, Swinburn BA. Metabolic predictors of obesity: cross-sectional versus longitudinal data. Int J Obes 1993; 17 (suppl 3): S28-S31.
14. Schwartz MW, Boyko EJ, Kahn SE, Ravussin E, Bogardus C. Reduced insulin secretion: An independent predictor of body weight gain. J Clin Endo Metab. 1995; 44: 147-151.