

## The Role of Carbohydrates in Insulin Resistance<sup>1</sup>

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**ABSTRACT** Insulin resistance is a metabolic disorder that is increasing worldwide and is associated with some of the most common diseases affecting modern societies including diabetes, hypertension, obesity and coronary heart disease. Although pharmacologic approaches to managing insulin resistance are being advocated by some, public health approaches involving changes in diet and physical activity are attractive because of their lower cost and risk. We briefly summarize some new information on the mechanisms that mediate insulin's many biological actions and examine the effects of dietary carbohydrates on insulin sensitivity. Specifically, we summarize some of the information available on the effects of simple sugars, complex carbohydrates including fiber, slowly digested starch and the general concept of glycemic index. The available data support the idea that consumption of diets high in total carbohydrate does not adversely affect insulin sensitivity compared with high fat diets. Animal data suggest that simple sugars, in particular fructose, have adverse effects on insulin action, but adverse effects have not been shown conclusively in humans. Increased intake of dietary fiber appears to improve insulin action and may protect against the development of diabetes. The effects of diets with high or low glycemic index on insulin action are controversial at this time. For firm conclusions to be reached, future studies must be of reasonable duration, be in defined populations and compare the effects of relevant doses of nutrients on specific endpoints of insulin action. *J. Nutr.* 131: 2782S–2786S, 2001.

**KEY WORDS:** • *insulin resistance* • *carbohydrate* • *sucrose* • *fiber* • *glycemic index*

The increasing prevalence of disorders associated with insulin resistance, including diabetes, obesity and hypertension (1), as well as the continuing public health threat posed by cardiovascular disease, has increased interest in the effects that alterations in diet composition have on insulin sensitivity. There are many problems in identifying relationships between diet composition and disease risk. The hypothesis that insulin resistance is a measurable intermediate step has provided the impetus for studies in this area. Although insulin resistance has been related to these disorders, the relationship is not the only way in which diet may affect the development or progression of these diseases. Additionally, in some populations, the relationship between insulin resistance and disease are not always seen. For example, not all studies show a relationship between insulin resistance and coronary artery disease in non-diabetic individuals (2). It is important to keep a clear sense of what the end goal is, presumably disease prevention or disease treatment, before assuming that nutritional intervention directed at reducing insulin resistance is desirable as a means of disease prevention. However, data supporting the association

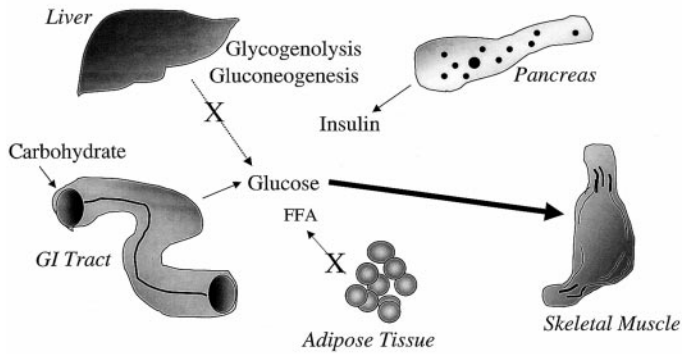
between insulin resistance and disease risk are strong enough and the types of dietary changes suggested practical enough that continuing research seems warranted. Although many studies have examined the relationship between total carbohydrates and carbohydrate subtypes in the diet and insulin sensitivity, many controversies remain (3). Some of the difficulties in this area stem from the complexities of insulin action.

### *Insulin resistance: what is it and how is it measured?*

The traditional view of insulin action places this hormone at the center of multiple organ adaptations to the ingestion of nutrients, in particular, dietary carbohydrates (**Fig. 1**). Insulin stimulates the disposal of ingested glucose into skeletal muscle and adipose tissue and decreases the production of glucose by the liver by reducing glycogenolysis and gluconeogenesis. In addition, insulin suppresses the release of nonesterified fatty acids from adipose tissue by suppressing lipolysis. A number of methods have been used to assess insulin sensitivity in animals and humans. These include measures of fasting insulin and glucose concentrations, the homeostatic model, glucose or insulin area under the curve after ingestion of glucose, the frequently sampled intravenous glucose tolerance test, the hyperinsulinemic euglycemic clamp, graded glucose infusions, and cellular and molecular studies of insulin signaling. The more complex studies provide more detailed insights into tissue-specific insulin actions but are not useful for large-scale epidemiologic studies.

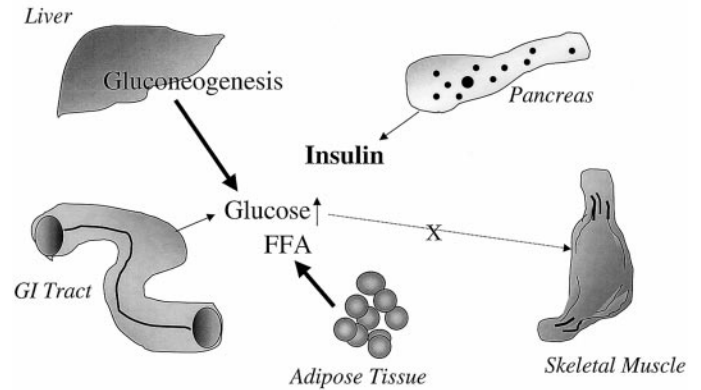
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‘Classical Insulin Actions’



**FIGURE 1** Classical insulin actions. Abbreviations: FFA, free fatty acids; GI tract, gastrointestinal tract.

Insulin Resistance



**FIGURE 2** Insulin resistance. Abbreviations: FFA, free fatty acids; GI tract, gastrointestinal tract.

Recent studies in mice in which insulin receptors have been removed from specific tissues including skeletal muscle (4), adipose tissue, liver, pancreatic  $\beta$  cells ( $\beta$  cell-specific insulin receptor knockout; BIRKO)<sup>2</sup> (5) and the brain (neural insulin receptor knockout; NIRKO) (6) have emphasized the interdependence of these tissues in maintaining normal glucose levels. The surprising finding that mice lacking insulin receptors in skeletal muscle have peripheral insulin resistance but normal fasting glucose and insulin levels as well as normoglycemia and insulinemia after glucose ingestion demonstrates the potential weakness of these latter measures in demonstrating insulin resistance. In addition, the presence of obesity, mild insulin resistance and hyperinsulinemia in NIRKO mice demonstrates the important role of the brain as an insulin-sensitive organ. BIRKO mice lose insulin secretory capacity and develop a syndrome that looks type 2 diabetes. This finding suggests that insulin resistance in the  $\beta$  cell could play a role in the insulin deficiency seen in type 2 diabetes.

Although experimental studies using the euglycemic clamp and oral glucose tolerance test have focused attention on the physiology of skeletal muscle and liver (Fig. 2), these recent knockout experiments emphasize the critical role of the pancreas, brain and adipose tissue as insulin-sensitive organs (Fig. 3). Unfortunately, it is difficult to assess insulin sensitivities in these tissues in humans in vivo. Insulin resistance is likely not the same in all tissues as it develops. It is becoming increasingly clear that sequential alterations in the relative insulin sensitivities of these critical tissues may be very important in the development of disease states such as obesity and diabetes. Unfortunately, most studies of diet and insulin sensitivity have not examined the effects of altering the diet on tissue specific insulin actions.

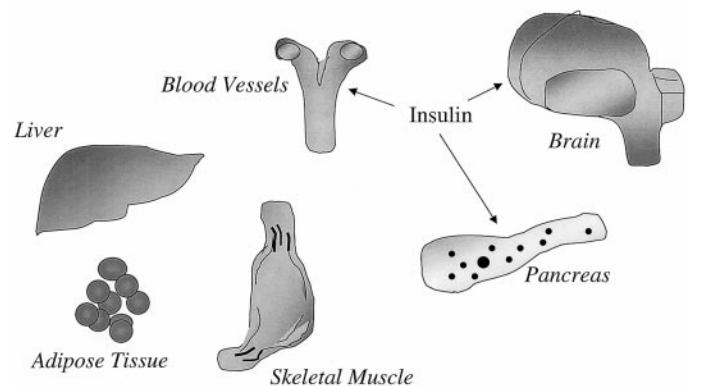
**A second level of complexity: the cell that is the target for insulin action**

Over the past 10 years, there has been an explosion of new information about the signaling pathways involved in transducing insulin’s multiple actions on different tissues (7,8). After insulin binds to its receptor on the cell membrane of the responsive cell, a variety of signaling events occur (Fig. 4). The insulin receptor autophosphorylates via tyrosine residues, which leads to an increase in insulin receptor kinase activity

and to phosphorylation of a variety of insulin receptor substrates. These phosphorylated insulin receptor substrates then interact sequentially with downstream proteins to stimulate glucose uptake through the translocation of glucose transporters (GLUT4) to the cell surface, alterations in gluconeogenesis through changes, for example, in the expression of relevant enzymes, increased cell growth, suppression of lipolysis and alterations in glycogen synthesis. Evidence is increasing that in settings of insulin resistance, certain intracellular signaling pathways are more affected (resistant to stimulation by insulin) than others. This means that within a single tissue, certain insulin actions may be more resistant than others to hormone stimulation. The mechanisms by which changes in nutrient intake alter insulin-signaling events within relevant tissues remain obscure. In addition, it is not clear how genetic variation in relevant gene products along these insulin-signaling pathways might alter the relationships between nutrients and insulin action in particular tissues.

In summary, insulin resistance is not a simple phenotype. Different tissues may have different levels of sensitivity to insulin, and within a single tissue, certain insulin actions may be more or less involved in the process of insulin resistance. It is easy to imagine how this complexity in the biology of insulin action might lead to complexity in interpreting studies that try to examine the relationships between alterations in dietary composition and insulin action. It seems unlikely that any

‘Newly Appreciated Insulin Actions’

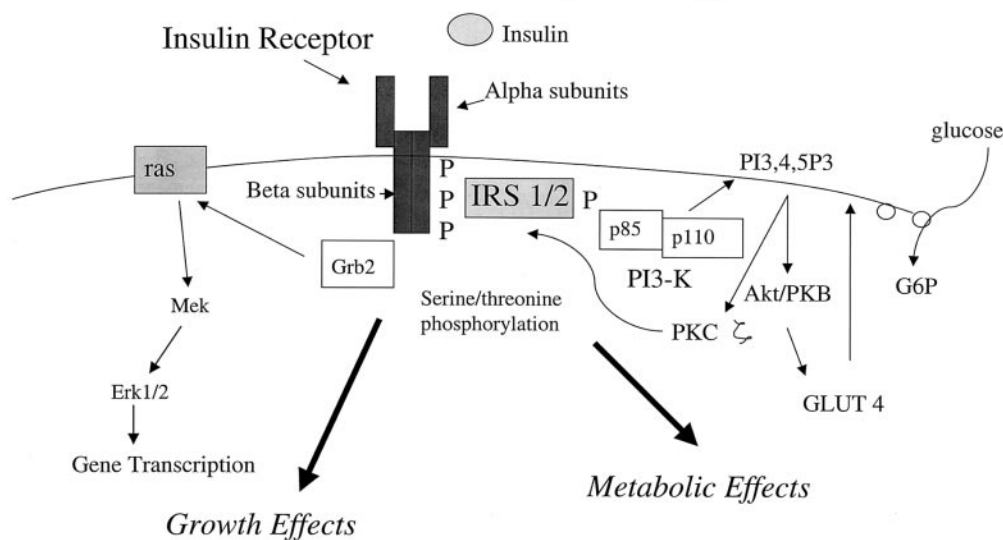


**FIGURE 3** Newly appreciated insulin actions.

<sup>2</sup> Abbreviations used: BIRKO,  $\beta$  cell-specific insulin receptor knockout; GI, glycemic index; NIRKO, neural insulin receptor knockout.

# Insulin Signaling

**FIGURE 4** Insulin signaling. Abbreviations: IRS, insulin receptor substrate; PI3-K, phosphoinositide-3 kinase; PK, protein kinase; erk, extracellular signal-regulated kinase; GLUT 4, glucose transporter 4.



simple relationship between a change in the composition of the diet and a change in insulin action will emerge. Rather, the effects of dietary changes on insulin action within specific groups that are most likely to experience adverse health effects should be sought. As detailed genetic information emerges on insulin resistance, this new information should be incorporated into nutritional studies.

### Macronutrient composition of the diet in insulin sensitivity

When the relationship between a change in the diet and insulin sensitivity is examined, the first problem encountered is that any change in one component of the diet is accompanied by reciprocal changes in other components of the diet. When the effect of dietary carbohydrates on insulin action is examined, it is important to note what other changes are being made in the diet when carbohydrate is altered. Early experiments in humans examined the effect on insulin action of altering the relative amounts of dietary carbohydrate and fat. As far back as 1935, Himsworth found that the ability of insulin to lower blood glucose was improved as dietary carbohydrate increased. That is, a low carbohydrate, high fat diet was associated with a reduced ability of insulin to reduce plasma glucose; conversely, a low fat, high carbohydrate diet was associated with an improvement in insulin's ability to stimulate glucose disposal. This general finding has been seen in animal studies and more recent human studies as summarized in the excellent review by Daly et al. (9). Using the euglycemic, hyperinsulinemic clamp method, Swinburn compared the effects of a high carbohydrate diet with a lower carbohydrate diet in Pima Indians (9). In this study, fasting insulin and glucose levels were improved despite no change having occurred in insulin action as measured by the hyperinsulinemic clamp.

Recent epidemiologic studies have looked at the relationship between diet composition and the onset of type 2 diabetes, a relationship that may involve changes in insulin action as well as insulin secretion. In the San Luis Valley study, no relationship was found between dietary carbohydrate and either hyperinsulinemia or the onset of frank diabetes (10). In fact, there was a trend for an inverse relationship. However, a significant relationship occurred between dietary fat and newly

diagnosed cases of diabetes. The strength of this study comes from its prospective design, careful diet histories and accurate case identification. Three other recent studies, the Health Professionals Follow-Up Study (11), the Nurses Health Study (12) and the Iowa Women's Health Study (13), looked at large populations of men and women and examined the relationship between diet composition and the onset of diabetes. These studies also failed to show a relationship between total carbohydrate intake and development of diabetes. Most recently, Swinburn et al. (14) demonstrated in a prospective study that a low fat (26% of energy), high carbohydrate (54% of energy) diet was associated with improved glucose tolerance and reduced progression to diabetes in a group of individuals with impaired glucose tolerance.

Taken together, these data support the idea that high carbohydrate diets, at the very least, do not adversely affect insulin sensitivity and may be beneficial for insulin sensitivity. On the contrary, high intakes of dietary fat, particularly saturated fat, do appear in some of these studies to be associated with a decline in insulin sensitivity.

### Simple sugars

Simple sugars include the monosaccharides (glucose, fructose and galactose) and the disaccharides (sucrose, maltose and lactose). Many animal studies have examined the relationship between insulin action and high intakes of fructose and sucrose (15). Studies in rats have generally demonstrated that high intake of sucrose (18–70% of energy) or fructose (15–60% of energy) produce a decline in insulin sensitivity in the liver and later in peripheral tissues (16). An exception to this finding is a study done in female rats that found no association between increased consumption of sucrose and insulin resistance (17). In general, these studies have demonstrated that the adverse effects of sucrose and fructose are a function of the dose used and duration of exposure such that if a lower dose is used, the duration of exposure must be longer to produce the effect. In addition, the effects of sucrose on insulin action appear to be less in older obese rats that already have a moderate degree of insulin resistance, and in rats that are already insulin resistant as a result of consumption of a high fat diet (18). Fructose appears to be avidly taken up and

metabolized by the liver. This uptake and metabolism produce a metabolic state characterized by increased glucose uptake by the liver, which leads to a variety of cellular events, such as changes in the expression of the gluconeogenic enzymes that produce insulin resistance.

Studies in humans examining the ability of dietary sucrose to produce insulin resistance have not been nearly as convincing (3). Studies in both normal adults and adults with type 2 diabetes have fairly consistently shown no effect on insulin sensitivity of isoenergetic substitution of sucrose or fructose for starch. Many of these studies had relatively few subjects and were of short duration. Isolated studies have shown adverse effects of dietary sucrose, but these are the exception rather than the rule. Both fructose and sucrose are associated with lower glucose excursions after ingestion, and some recommendations have even advocated the use of fructose as a beneficial sweetener for individuals with type 2 diabetes. The most recent nutritional recommendations of the American Diabetes Association do not advocate or discourage the use of these sweeteners on the basis of available data. They do caution about the development of hypertriglyceridemia with high fructose diets. Epidemiologic studies have also failed to show a relationship between fructose or sucrose consumption and the development of type 2 diabetes.

How can the discrepant results in animals and humans be reconciled? The studies done in rats suggest that if a low dose of sucrose or fructose is used, prolonged exposure is necessary to produce insulin resistance. In addition, the animal studies suggest that if adult animals or animals with preexisting insulin resistance are examined, the effects of these nutrients are reduced. Because most studies in humans have been done in older adult populations and many of the studies have been done in subjects with type 2 diabetes whose liver glucose production is already markedly elevated, it is perhaps not surprising that no effects of these nutrients has been seen.

In summary then, if sucrose has deleterious effects in humans, they are most likely to be produced in younger individuals with moderate-to-high sucrose and fructose intakes over a prolonged period. Information from human studies is not sufficient to conclusively demonstrate any adverse effects of sucrose or fructose in the diet. However, studies adequate to test this idea in younger individuals have not been done.

### **Complex carbohydrates**

Complex carbohydrates are long polymers of glucose or other monosaccharides. The nomenclature attributed to these compounds can be confusing. Polymers of glucose can occur in a branched form known as amylopectin or a linear form known as amylose. Resistant starch is a term used for starches that are not directly absorbed but travel to the large intestine where they can be fermented by gut flora to produce short-chain fatty acids such as butyrate and propionate. Starch can be processed to increase the relative amount of resistant starch. Other kinds of carbohydrate polymers with nonglucose monomers such as xylose are indigestible. These complex carbohydrate molecules are the constituents of soluble or insoluble fiber. They include lignin,  $\beta$  glucan, guar gum and hemicelluloses such as arabinoxylan, a major component of cereal fiber. Fiber provides minimal energy but may interact with other nutrients in the gastrointestinal tract.

In the past, complex carbohydrate consumption was thought to possibly be beneficial because of the delayed absorption of these carbohydrate polymers. However, careful studies have demonstrated that many forms of starch are absorbed as rapidly as pure glucose. The rate of absorption of

complex carbohydrate depends on its chemical structure as well as methods of preparation and associated constituents of the diet. Because of its greater access to amylase, amylopectin is more rapidly digested and absorbed than amylose. Conversely, amylose appears to be more slowly absorbed and may form helices that may interact with dietary fat, slowing its absorption as well. Studies done in laboratory rats have demonstrated that high amylose diets appear to have beneficial effects on insulin sensitivity compared with high amylopectin diets (19). Only limited data exist on amylose-rich diets in humans. What data are available suggest that there are minimal effects on insulin sensitivity, but that meals containing amylose may promote fat oxidation relative to meals containing amylopectin. Obtaining accurate information on the amylose content of various foods is very difficult, and the availability of foods that are enriched in amylose is limited.

The glycemic index (GI) has been proposed as a way in which to categorize carbohydrate foods as those that are rapidly absorbed (high GI) or more slowly absorbed (low GI) on the basis of the postingestion glucose area under the curve. Several recent studies suggested that diets that have a low GI may improve insulin sensitivity (20) and that consuming a low GI diet may be associated with a lower risk for type 2 diabetes (11,12). Other studies have not shown a relationship between GI and risk for diabetes (13). In a recent, carefully done interventional study, Kiens was unable to show any benefit to insulin sensitivity of a low GI diet as measured by the gold standard method, the euglycemic hyperinsulinemic clamp [reviewed in (3)]. The subjects in this study were young, healthy, highly active males. The test chosen to measure insulin action examined primarily skeletal muscle insulin sensitivity. The beneficial effects of a low GI diet may be targeted primarily at the pancreas. High GI diets may tax the insulin secretory capacity of a pancreas that has acquired some limitation in this parameter. If this is true, diets with a high GI might exert their adverse effects late in the progression to type 2 diabetes. The GI has been criticized for not taking into account the interaction between the carbohydrate foodstuffs and other nutrients in the meal such as fat and protein. However, a number of recent studies have demonstrated that meals can be constructed of foods with either a high or low GI and that the postmeal glucose excursion generally follows what would be predicted from the GI of the individual foods. It is somewhat confusing, however, that the simple sugars sucrose and fructose have a very low GI and have very little stimulatory effects on insulin secretion and yet are thought to have adverse effects on insulin action. Many issues remain concerning the clinical utility of the GI, and questions remain concerning the nature of the observed effects and the underlying mechanisms.

Ingestion of foods high in dietary fiber content appears to be associated with modest beneficial effects on insulin sensitivity. Three studies have shown fiber consumption to be associated with a reduced risk of type 2 diabetes (13,21,22). Fiber was shown to slow the postprandial rise in glucose and improve glycemic control in people with diabetes. Although there are difficulties in the nomenclature related to dietary fiber, information on the fiber content of foods is available on package labels, and there are accepted consumption guidelines. This puts fiber in a better position than amylose or GI with regard to implementing dietary change using existing food availability and labeling. In summary, it appears that the ingestion of resistant, more slowly absorbed starch may have beneficial effects on insulin sensitivity; however, data are not adequate to support widespread use of these foods to treat or prevent disease. The data relating to fiber consumption appear to be stronger, and thus it seems reasonable to advocate

moderate fiber (20–30 g/d) consumption in any diet designed to improve insulin action.

### Summary and conclusions

Insulin resistance and the diseases associated with it represent major public health challenges in the United States and around the world. Although it would be attractive to find an ideal diet for the prevention and treatment of insulin resistance states, this is probably an unrealistic expectation. Knowledge gained from both animal and human studies about the effect of simple and complex carbohydrates on insulin action is increasing. However, any change in the carbohydrate composition of the diet may produce reciprocal changes in other parts of the diet.

It is important to remember that on balance, increased energy intake and positive energy balance may be the nutritional factors that are most to blame for insulin resistance through the production of obesity. In addition, energy restriction, independent of the composition of the diet, may be the best nutritional approach to treating insulin resistance.

Intake of dietary fat, particularly saturated fat, appears to be associated with insulin resistance in animals (23) and humans (21) and may predispose to the development of diabetes (10). It seems prudent at this time to advocate increased fiber consumption. Resistant starch or low GI diets may ultimately prove to have beneficial effects at some stage in the development of type 2 diabetes, but this remains controversial. Although simple sugars appear to cause insulin resistance in rats, adverse effects in humans have not been demonstrated conclusively. Future studies should use appropriate doses of these nutrients fed over moderate periods of time to populations presumed to be the most susceptible to their effects. These populations might be the young in the case of simple sugars and those with preexisting insulin resistance in the case of complex carbohydrate and fiber. Clear relationships may not emerge until it is possible to obtain a more accurate phenotype or even genotype of subjects because genetic heterogeneity likely underlies the heterogeneous response to these diets.

Studies relating specific foods to specific disease states may provide the most useful information for nutrition policy decisions. If the relationship between a nutrient and insulin sensitivity is to be examined, then specific measures of insulin action in the tissue that is likely to be affected or likely to be related to disease risk should be undertaken. Simply using insulin and glucose levels is unlikely to provide meaningful insights into these relationships. The relationships between diet and insulin action remain an important area for future investigation.

### LITERATURE CITED

1. Reaven, G. M. (1988) The role of insulin resistance in human disease. *Diabetes* 37: 1595–1607.

2. Ginsberg, H. N. (2000) Insulin resistance and cardiovascular disease. *J. Clin. Invest.* 106: 453–458.
3. Wolever, T.M.S. (2000) Dietary carbohydrates and insulin action in humans. *Br. J. Nutr.* 83 (suppl. 1): S97–S102.
4. Bruning, J. C., Michael, M. D., Winnay, J. N., Hayashi, T., Horsch, D., Accili, D., Goodyear, L. J. & Kahn, C. R. (1998) A muscle specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. *Mol. Cell* 2: 559–569.
5. Kulkarni R. N., Bruning, J. C., Winnay, J. N., Postic, C., Magnuson, M. A. & Kahn, C.R. (1999) Tissue specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* 96: 329–339.
6. Bruning, J. C., Gautam, D., Burks, D. J., Gillette, J., Schubert, M., Orban, P. C., Klein, R., Krone, W., Muller-Wieland, D. & Kahn, C. R. (2000) Role of brain insulin receptor in control of body weight and reproduction. *Science* (Washington, DC) 289: 2122–2125.
7. Withers, D. J. & White, M. (2000) The insulin signaling system—a common link in the pathogenesis of type 2 diabetes. *Endocrinology* 141: 1917–1921.
8. Le Roith, D. & Zick, Y. (2001) Recent advances in our understanding of insulin action and insulin resistance. *Diabetes Care* 24: 588–597.
9. Daly, M. E., Vale, C., Walker, M., George, K., Alberti, M. M. & Mathers, J. C. (1997) Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications. *Am. J. Clin. Nutr.* 66: 1072–1085.
10. Marshall, J. A., Hoag, S., Shetterly, S. & Hamman, R. F. (1994) Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. *Diabetes Care* 17: 50–56.
11. Salmeron, J., Ascherio, M., Rimm, E. B., Colditz, G. A., Spiegelman, D., Jenkins, D. J., Stampfer, M. J., Wing, A. L. & Willett, W. C. (1997) Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 20: 545–550.
12. Salmeron, J., Manson, J. E., Stampfer, M. J., Colditz, G. A., Wing, A. L. & Willett, W. C. (1997) Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J. Am. Med. Assoc.* 277: 472–477.
13. Meyer, K. A., Kushi, L. H., Jacobs, D. R., Slavin, J., Sellers, T. A. & Folsom, A. R. (2000) Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am. J. Clin. Nutr.* 71: 921–930.
14. Swinburn, B. A., Metcalf, P. A. & Ley, S. J. (2001) Long term (5-year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* 24: 619–624.
15. Storlien, L. H., Higgins, J. A., Thomas, T. C., Brown, M. A., Wang, H. Q., Huang, X. F. & Else, P. L. (2000) Diet composition and insulin action in animal models. *Br. J. Nutr.* 83 (suppl. 1): S85–S90.
16. Pagliassotti, M. J. & Prach, P. A. (1995) Quantity of sucrose alters the tissue pattern and time course of insulin resistance in young rats. *Am. J. Physiol.* 269: R641–R646.
17. Horton, T. J., Gayles, E. C., Prach, P. A. & Pagliassotti, M. J. (1997) Female rats do not develop sucrose-induced insulin resistance. *Am. J. Physiol.* 272: R1571–R1576.
18. Pagliassotti, M. J., Gayles, E. C., Podolin, D. A., Wei, Y. & Morin, C. L. (2000) Developmental stage modifies diet-induced peripheral insulin resistance in rats. *Am. J. Physiol.* 278: R66–R73.
19. Higgins, J. A., Brand Miller, J. C. & Denyer, G. S. (1996) Development of insulin resistance in the rat is dependent on the rate of glucose absorption from the diet. *J. Nutr.* 126: 596–602.
20. Ludwig, D. S., Pereira, M. A., Kroenke, C. H., Hilner, J. E., VanHorn, L., Slattery, M. L. & Jacobs, D. R. (1999) Dietary fiber, weight gain, and cardiovascular risk factors in young adults. *J. Am. Med. Assoc.* 282: 1539–1546.
21. Marshall, J. A., Bessesen, D. H. & Hamman R. F. (1997) High saturated fat and low starch and fiber are associated with hyperinsulinemia in a non-diabetic population: the San Luis Valley Diabetes Study. *Diabetologia* 40: 430–438.
22. Boeing, H., Weisgerber, U. M., Jeckel, A., Rose, H. J. & Kroke, A. (2000) Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population: cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. *Am. J. Clin. Nutr.* 71: 1115–1122.
23. Storlien, L. H., Baur, L. A., Kriketos, A. D., Pan, D. A., Cooney, G. J., Jenkins, A. B., Calvert, G. D. & Campbell, L.V. (1996) Dietary fats and insulin action. *Diabetologia* 39: 621–631.