Regulation of Nutrient Metabolism and Energy Expenditure

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The requisites for energy expenditure are covered mainly by two major substrates, glucose and free fatty acids (FFA). Their regulation and metabolism differ. After carbohydrate ingestion, glucose is rapidly oxidized or stored in muscles and liver. There is a constant alternance between glucose storage as glycogen after meals and glycogen mobilization in the postabsorptive state when plasma glucose has returned to the basal state. Impairment of this alternance, in particular when glycogen stores are not being used, may lead to glucose intolerance and insulin resistance. Ingestion of lipids is not followed by an immediate increase in lipid oxidation, but FFA are stored as triglycerides in different tissues. Lipolysis occurs in the fasting state from tissue triglycerides and favors lipid oxidation. Lipid oxidation is typically increased in obesity. The preferential use of FFA from triglyceride stores for energy expenditure in obesity is responsible for the decrease in glucose mobilization from glycogen stores. This leads to a negative feedback of muscle and liver glycogen on glycogen synthase activity and consequently on glucose storage. It results in glucose intolerance after carbohydrate ingestion. Diabetes develops in obesity, usually after a long period of glucose intolerance, when glycemia does not return to the basal state. In obesity, glucose intolerance and insulin resistance can be prevented, or if already existing, can be decreased by stimulating glycogen mobilization by exercise, thermogenesis-stimulating drugs, and weight loss, which reduces fat stores and decreases lipid oxidation.

BASAL METABOLIC RATE (BMR), physical exercise, and thermogenesis represent the three components of energy expenditure in humans. In sedentary individuals, BMR represents 65% to 75% of total energy expenditure.[1] It predominantly depends on the size of fat-free mass, with which it positively correlates.[2] Physical activity varies according to the behavior of the individual. Thermogenesis, defined as the energy expenditure above BMR in a resting subject, is dependent on food intake and other factors such as caffeine, smoking, exposure to cold, etc. Ingestion of nutrients causes an increase in energy expenditure that varies with the composition and amount of the diet.

Energy needs, both in the basal state and during exercise, are covered by two major substrates: glucose and free fatty acids (FFA). Protein oxidation is related to protein intake and contributes 10% to 15% of total energy expenditure. Glucose and FFA can be considered interchangeable in the intermediary metabolism of most tissues, but the brain relies almost exclusively on glucose metabolism. Diet composition affects nutrient oxidation by making substrate oxidation partly reflect composition of the diet. Hill et al[3] showed that large and rapid shifts in substrate oxidation rates can be measured by a whole-room calorimeter without affecting total energy expenditure.

Glucose is an energy substrate for all organs and tissues. A large portion is consumed in the brain and nervous tissues, since these tissues do not use FFA. The same is true for blood cells. In contrast to these tissues, other tissues, especially skeletal muscle, can use FFA alternatively for their energy needs.

Metabolic pathways that lead to glucose oxidation and storage are regulated by enzymatic systems that are stimulated by the substrates and inhibited by the products. This is demonstrated in particular by the increase in glucose oxidation and storage after a carbohydrate-containing meal and by inhibition of glycogen synthesis via excess intracellular glycogen. This basic regulation is under the control of insulin, which stimulates the storage of energy substrates, on one hand, and the so-called counterregulatory hormones, especially epinephrine and glucagon, which stimulate mobilization of substrates when there is a need for energy, on the other.

REGULATION OF GLUCOSE METABOLISM

Carbohydrate ingestion or glucose administration is rapidly followed by an increase in glucose oxidation and by storage of glucose as glycogen. The need of insulin for glucose uptake in insulin-dependent tissues plays a major role in reserving glucose for the tissues, for which it represents an absolute necessity. In the basal state, when plasma glucose is low, glucose uptake in muscles and adipose tissue is prevented by the absence of an increase in insulin, thus reserving glucose for nervous tissue and blood cells. It is only in the postprandial state that the parallel increase in insulinemia and glycemia allows glucose to be taken up in muscle and adipose tissue.

Glucose oxidation starts rapidly after carbohydrate ingestion. It often remains high after glycemia and insulinemia have returned to basal values, which suggests that glucose oxidation continues from the newly-filled glycogen stores. The kinetics of this metabolic pathway are influenced by the amount of carbohydrate ingested.[4] In skeletal muscle, glucose from glycogen stores is consumed in situ, since glucose cannot be released into the circulation. Lactate can leave muscle to be used by other tissues. In tissues that do not depend on insulin, glucose is used according to energy needs. Exercise stimulates glucose oxidation by increasing energy expenditure. Conversely, the increased use of FFA as a substrate for oxidation in muscle decreases glucose oxidation. Both pathways of glucose and fatty acid oxidation end up in the citric acid cycle (Fig 1). Randle et al[5,6] reported an inhibition of pyruvate dehydrogenase and phosphofructokinase activities by metabolites of the citric acid cycle. This inhibition of glucose oxidation plays an

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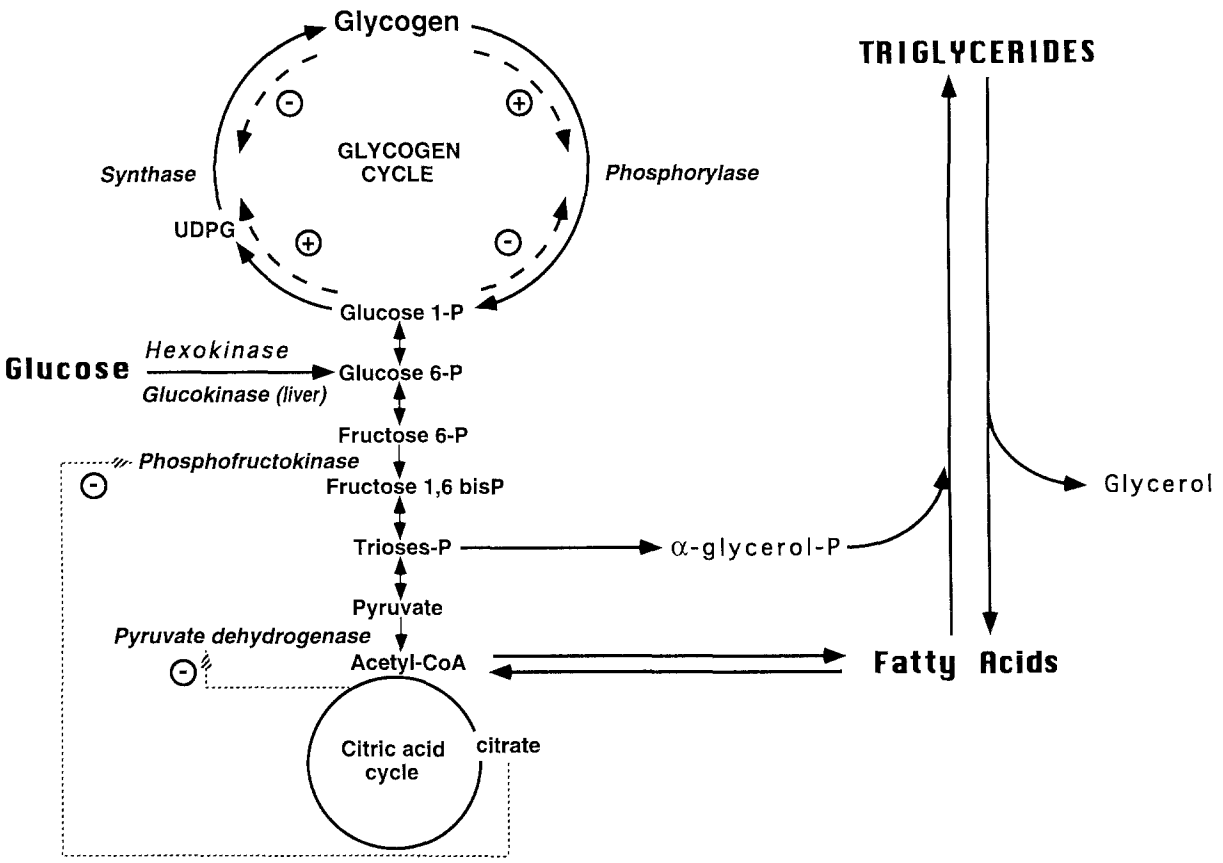

Fig 1. Metabolic scheme demonstrating relationship between glucose and fatty acid metabolism in muscle. The double regulation of glycogen synthase and phosphorylase activities by changes in glucose-6-phosphate (glucose 6-P) and glycogen concentrations are also represented. The increase in glucose 6-P and insulin stimulates glycogen synthase activity while inhibiting glycogen phosphorylase activity. Conversely, an increase in glycogen concentration inhibits glycogen synthase activity while stimulating glycogen phosphorylase activity.

important role in situations where FFA utilization is excessive, as is the case in obesity.[7]

Glucose storage represents the main fraction of glucose uptake.[8] Fifty percent to 70% of a glucose load is taken up by muscles and 30% to 50% by liver.[9,10] The cost of converting glucose to glycogen corresponds to approximately 5% of the glucose energy content, but the real cost is greater than that of direct glycogen synthesis.[2] As demonstrated by Shulman et al,[11] only one third of liver glycogen repletion occurs via the direct conversion of glucose. Glycogen formation via conversion of glucose to three-carbon intermediates such as lactate consumes more energy than the direct pathway.

The glycogen cycle consists of the storage of glucose as glycogen and its release from glycogen stores (Fig 1). This occurs essentially in muscles and liver and corresponds to the alteration of glycogen synthesis in the postprandial state and glycogen mobilization that follows (Fig 2). With the increase in glycemia and insulinemia after a meal, synthase *b*, the inactive form of glycogen synthase, is activated by dephosphorylation to synthase *a*, the active form, as a consequence of allosteric activation by glucose-6-phosphate. Glycogen synthase *a* catalyzes glycogen synthesis, which leads to glucose storage. Simultaneously, inactivation of phosphorylase occurs as the result of allosteric inhibition by glucose-6-phosphate and glucose, which produces the inhibition of glycogen mobilization.[12] When glycemia has returned to the basal level, this inhibition is released and glycogen phosphorylase is activated, permitting glucose mobilization from glycogen stores.

The stimulation of glycogen synthase and glycogen phosphorylase activities, which occur in succession, may also be inhibited by a series of negative feedback mechanisms, as suggested by recent studies.[13] When glucose oxidation is inhibited, as can be the case in the resting state when fatty acids are being used in preference to glucose, the high levels of glucose 6-phosphate and glucose may maintain their inhibition of glycogen phosphorylase activity, thus preventing glycogen mobilization. This in turn may inhibit glycogen synthase activity, as a consequence of the inhibition of the increased intracellular glycogen concentration on glycogen synthase activity.[12] Therefore, it may reduce or even block the activity of the glycogen cycle. The resulting decrease in glycogen storage will cause glucose intolerance.

Glucose storage as glycogen is a limited process. Accumulation of this polysaccharide ceases when a concentration of approximately 60 mg/g liver or 10 to 20 mg/g muscle has been reached.[14,15] Inhibition of glycogen synthase activity appears to be gradual with the progressive increase in glycogen concentration. Both processes of stimulation of

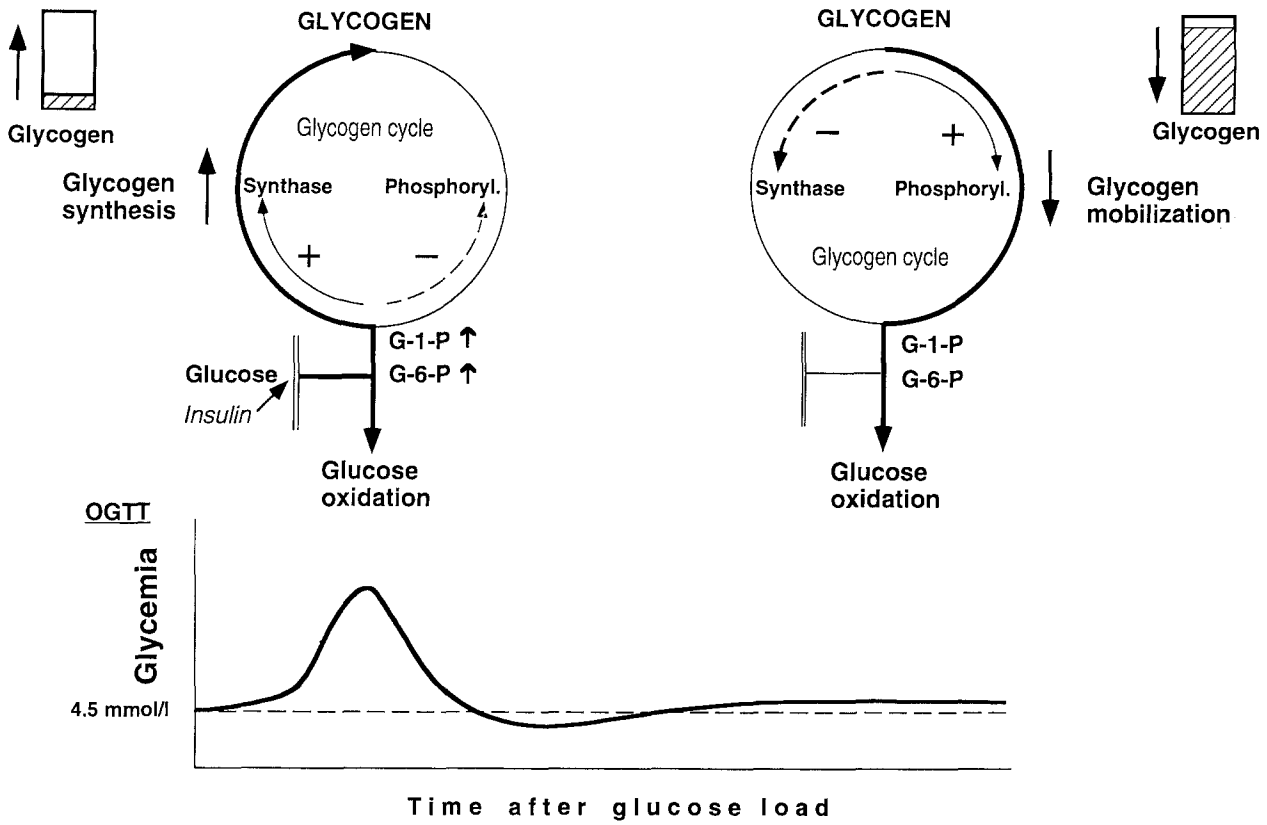

Fig 2. Physiologic regulation of glycogen synthesis and breakdown. Left, after a glucose load: The increase in plasma glucose and insulin concentrations is followed by an increase in glucose-6-Phosphate (G-6-P) and glucose-1-Phosphate (G-1-P), which stimulates glycogen synthase activity and consequently glycogen synthesis while inhibiting glycogen phosphorylase activity. Right, after the return of glycemia to basal levels: Inhibition of glycogen phosphorylase activity by the increased concentration of G-6-P is discontinued while, in contrast, the high intracellular glycogen concentration stimulates this enzymatic activity. This stimulates glycogen breakdown and mobilization of glucose for oxidative purposes. Simultaneously, the increased glycogen concentration might inhibit glycogen synthase activity.

glycogen synthesis by an increase in plasma glucose and insulin concentrations (anterograde regulation) and inhibition of glycogen synthesis as a consequence of inhibition of glycogen mobilization (retrograde regulation) are occurring through two different metabolic pathways.[16] They may proceed simultaneously when glycogen concentration has not reached its maximum. This may explain the observation of overcoming resistance to glucose storage by an increase in plasma insulin concentration, as seen in nondiabetic obesity with or without glucose intolerance.[13]

GLUCONEOGENESIS

An important function of the liver resides in the delivery of glucose to the bloodstream, providing glucose to the organs that need this substrate as their sole source of energy. Glucose delivered by the liver comes either from the glycogen stored in the liver after meals or from gluconeogenesis. Gluconeogenesis allows the production of glucose from a nonglucose origin. The main precursors are lactate, glycerol, and alanine, which are degradation products of carbohydrate, fat, and protein metabolism, respectively. Gluconeogenesis occurs according to delivery of precursor substrates to the liver.[17] The cost of conversion of proteins to glucose is particularly high, and the thermogenic response to protein ingestion or amino acids infusion is approximately 25% to 40% of the energy content of the nutrient load, depending on the metabolic fate of the amino acids.[18] While part of gluconeogenesis goes directly to the bloodstream to release glucose, another part is stored as glycogen.[19] As in the muscle, glycogen synthesis and breakdown are regulated in the liver by an anterograde mechanism that stimulates glycogen synthesis and thereafter glycogen breakdown, and by a retrograde mechanism that inhibits both of them. An increase in glucose 6-phosphate, as can occur when glycemia is increased above the basal level, is expected to inhibit glycogen mobilization and, with the increase in intracellular glycogen concentration, glycogen synthesis. As a consequence, glucose originating from gluconeogenesis would be diverted directly to the bloodstream, thus increasing the blood glucose concentration even more.

REGULATION OF LIPID METABOLISM

In contrast to carbohydrates, which can only be stored in limited quantity, the human body can accommodate large amounts of fat. Excess energy is deposited almost exclusively as fat during periods when energy intake exceeds energy expenditure. Excess body fat, as in the case of

obesity, plays an important role in the regulation of lipid oxidation and has important interactions with carbohydrate metabolism and insulin sensitivity.

Lipids represent long-term energy storage. They are a condensed form of stored energy, containing 9.3 kcal (38.9 kJ) per gram as compared with 3.7 kcal (15.5 kJ) for glucose. In man, the major part of body fat has a dietary origin, since net de novo fat synthesis from carbohydrates is limited.[20] The cost of digesting, absorbing, and storing ingested fat corresponds to 2% to 4% of its energy content. The cost of lipogenesis from glucose represents the equivalent of 24% of the energy content of glucose converted into lipid.[2] In contrast to carbohydrates, fat ingestion is not immediately followed by an increase in lipid oxidation or energy production.[21] Lipids are stored as triglycerides in adipose tissue and different organs such as muscles and liver, where they can serve as an immediate source of energy.

After consumption of a fat-containing meal, dietary fat absorbed by intestinal cells is incorporated into chylomicrons. Liver cells transfer some triglycerides of chylomicrons to triglyceride-rich very–low-density lipoprotein particles. The remaining chylomicrons and very–low-density lipoprotein are hydrolyzed in the capillary circulation of several tissues to release FFA. This hydrolysis is under the control of the enzyme lipoprotein lipase. FFA can be stored as triglycerides in fat depots or oxidized for energy production. The increase in fat mass is generally accompanied by an increase in lipid oxidation.

Net lipid oxidation is regulated by both plasma FFA and insulin concentrations. In lean nondiabetic subjects, when the carbohydrate supply is increased, as occurs after ingestion of a carbohydrate-containing meal, the increased insulin and glucose concentrations stimulate both cellular glucose uptake and oxidation. In these conditions, the elevated insulin concentration inhibits hydrolysis of endogenous triglyceride and therefore fat oxidation in insulin-sensitive tissues and directs dietary fat toward triglyceride synthesis in adipocytes. In contrast, in the postabsorptive state, when carbohydrate supply is decreased, the decreased insulin concentrations and relative increase in lipolytic hormones (epinephrine, norepinephrine, glucagon, growth hormone, cortisol, etc.) stimulate hormone-sensitive lipase, which results in hydrolysis of triglycerides stored in adipose tissue and release of FFA for oxidation by insulin-requiring tissues. In this situation, utilization of triglycerides stored within skeletal muscle is also stimulated. In the postabsorptive state, approximately 50% of lipid oxidation can be accounted for by oxidation of the intramuscular triglyceride deposit.[22]

Lipid oxidation occurs essentially in muscles where FFA share with glucose the role of major energetic substrate. Lipids and glucose are both metabolized to acetylcoenzyme A before entering the citric acid cycle. Thus, when both substrates are being concomitantly metabolized, they compete with each other to enter the citric acid cycle and aerobic energy production (Fig 1).[5]

EFFECT OF OBESITY ON THE REGULATION OF NUTRIENT METABOLISM

Obesity is defined as an increase in body fat content. Characteristically, lipid oxidation is increased in both the basal and postprandial states, with a decreased suppression of lipid oxidation after an oral glucose tolerance test (OGTT).[7] The increase in lipid oxidation occurs as an early phenomenon and remains associated with obesity independently of its duration.[23] In obese individuals, the large amount of adipose tissue is responsible for the increase in FFA production[22] and consequently lipid oxidation. The increase in lipid oxidation is associated with a decrease in glucose oxidation, as expected from the inhibitory effect of lipid oxidation on glucose oxidation in skeletal muscle.

Insulin resistance is also observed early in the development of obesity, as can be demonstrated by the euglycemic insulin clamp technique. The decrease in glucose uptake, especially in glucose storage, observed in the euglycemic conditions of the clamp is compensated for during an OGTT by an increase in both plasma glucose and insulin responses to the load[24] (Fig 3). Glucose storage occurs

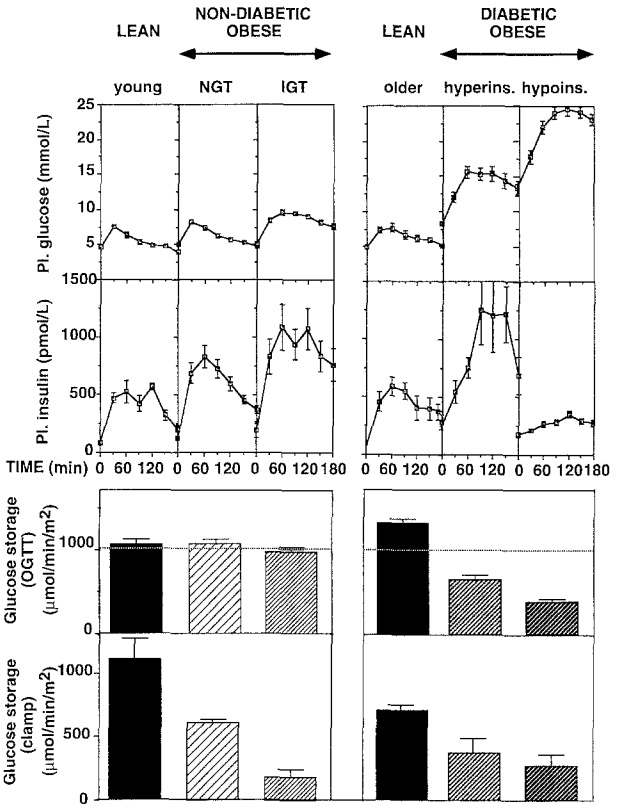

Fig 3. Glucose storage rate in nondiabetic obese and diabetic obese subjects during euglycemic clamp and OGTT. Note the marked impairment in glucose storage in the 2 nondiabetic obese groups (with normal glucose tolerance [NGT] and impaired glucose tolerance [IGT]) during the clamps and the absence of any change in glucose storage during OGTT. However, during OGTT, glucose storage occurs at higher glycemia (obese subjects with IGT) and higher insulinemia (obese subjects with NGT and IGT). In contrast, glucose storage in obese diabetic subjects is decreased during both the clamp and OGTT in the 2 diabetic obese groups. (Reprinted with permission.[13] © 1993 by Springer-Verlag.)

normally, but at high plasma glucose and insulin concentrations. This process is reversible, as demonstrated by the normalization, ie, the decrease, of plasma insulin and glucose responses to the glucose load after weight loss.[23] This suggests that insulin resistance observed in these conditions in obesity is essentially of metabolic origin, related to the excess in lipids as a substrate for energy expenditure at the expense of glucose.

Insulin resistance is generally accompanied by a reduced thermogenic response to carbohydrate administration. Golay et al[25] reported a decreased thermogenic response to glucose ingestion in obese subjects with insulin resistance. The lower thermic effect of glucose in the obese may be a consequence of the unstored glucose, which contributes to spare the energy needed to synthesize glycogen. However, the decrease in glucose-induced thermogenesis does not seem to play an important role in the development of obesity, since the thermogenic defect represents a smaller saving of energy than the increased BMR and the additional cost of weight-bearing physical activity generally present in obesity.[2]

The evolution from obesity with normal glucose tolerance to obesity with impaired glucose tolerance shows not only an increase in the glycemic response to a carbohydrate-containing meal, but also a longer duration of this glycemic increase.

EFFECT OF NON–INSULIN-DEPENDENT DIABETES MELLITUS OF THE OBESE ON THE REGULATION OF NUTRIENT METABOLISM

The prolongation of hyperglycemia as a compensatory mechanism allows one to overcome the resistance to glucose storage. In the obese, diabetes starts when glycemia has not returned to the basal level in the early-morning fasting state. In the period after the onset of diabetes, insulin secretion may be maintained for some time (non–insulin-dependent diabetes mellitus [NIDDM] with hyperglycemic response).[23,26] However, this insulin response decreases progressively and is replaced by a minimal insulin response in the presence of an elevated basal insulin secretion (NIDDM with hypoglycemic response). Here, as well, the major cause of diabetes resides in insulin resistance, differing from NIDDM of lean subjects, where a lack of insulin secretion is the major cause of hyperglycemia.[27,28]

REGULATION OF NUTRIENT METABOLISM, A BASIS FOR THERAPY

On the basis of these pathophysiologic considerations, treatment can be directed toward the cause of insulin resistance or aim to overcome insulin resistance by insulin.

In the first case, since the main cause of insulin resistance resides in the decrease in glycogen mobilization, therapy should be directed toward improvement of glycogen mobilization to decrease the resistance to glucose uptake, especially glucose storage. This can be accomplished by increasing energy expenditure through exercise[29] or by drugs that stimulate thermogenesis. Weight loss is a more causal therapy, which improves glucose uptake by decreasing the inhibitory effect of a prolonged increase in lipid oxidation on glycogen breakdown and glucose oxidation.

The other method uses the stimulatory effect of insulin on glycogen synthase activity to overcome the feedback inhibition of glycogen synthesis. Furthermore, by decreasing basal glycemia, insulin decreases the inhibitory effect of hyperglycemia on glycogen mobilization, thus restoring the anterograde function of the glycogen cycle. Insulin can be given as such, or be produced through drugs that stimulate its secretion. Weight loss may also improve insulin secretion when the decrease of plasma glucose allows insulin synthesis to be achieved in the pancreatic secretory granules and to be stored before being secreted.

CONCLUSIONS

Physiologic regulation of nutrient metabolism includes the alternance of energy storage and expenditure. Different nutrients vary in the amount of energy they contain, and the thermogenesis induced for digestion and storage of substrates as glycogen and triglycerides, the major forms of nutrient storage. Obesity develops when energy intake exceeds energy expenditure over a prolonged period. The decrease in utilization of glucose from glycogen stores, which is generally observed in obesity in the basal state, results in a series of feedback mechanisms that are the origin of a decrease in glucose uptake and insulin resistance. Therapy should tend to reintroduce the physiologic alternance of storage and mobilization of energy substrates.

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