Insulin Effects on Target Tissues

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Glucose levels in blood must be constantly maintained within a tight physiological range to sustain anabolism. Insulin regulates glucose homeostasis via its effects on glucose production from the liver and kidneys and glucose disposal in peripheral tissues (mainly skeletal muscle). Blood levels of glucose are regulated simultaneously by insulin-mediated rates of glucose production from the liver (and kidneys) and removal from muscle; adipose tissue is a key partner in this scenario, providing nonesterified fatty acids (NEFA) as an alternative fuel for skeletal muscle and liver when blood glucose levels are depleted. During sleep at night, the gradual development of insulin resistance, due to growth hormone and cortisol surges, ensures that blood glucose levels will be maintained within normal levels by: (a) switching from glucose to NEFA oxidation in muscle; (b) modulating glucose production from the liver/kidneys. After meals, several mechanisms (sequence/composition of meals, gastric emptying/intestinal glucose absorption, gastrointestinal hormones, hyperglycemia mass action effects, insulin/glucagon secretion/action, de novo lipogenesis and glucose disposal) operate in concert for optimal regulation of postprandial glucose fluctuations. The contribution of the liver in postprandial glucose homeostasis is critical. The liver is preferentially used to dispose over 50% of the ingested glucose and restrict the acute increases of glucose and insulin in the bloodstream after meals, thus protecting the circulation and tissues from the adverse effects of marked hyperglycemia and hyperinsulinemia.

postabsorptive postprandial glucose metabolism | fasting | insulin action secretion | liver | muscle | adipose tissue | incretins | meal sequence

1. Introduction

Food has major effects on physical health. Although there is an obvious need for energy to perform physical activities, energy requirements persist during rest. The substrates used by tissues as energy sources are carbohydrates, fat, and proteins. Although the energy yield of 1 g of fat is more than twice that of 1 g of carbohydrate or protein, tissues depend on glucose as the major energy source. With regard to the brain and red blood cells, glucose is the only fuel they use; therefore, they rely on the bloodstream to provide a constant supply [1].

Insulin plays a primary role in the regulation of glucose homeostasis via its effects on insulin-sensitive tissues: blood levels of glucose are regulated simultaneously by the rates of glucose production from the liver (and kidneys), and the rates of its removal from peripheral tissues (mainly skeletal muscle). Adipose tissue is a key partner in this scenario, providing nonesterified fatty acids (NEFA) as an alternative fuel for skeletal muscle, liver,

and kidneys when blood glucose levels are depleted. These mechanisms are supported by balanced adjustments in insulin secretion to keep the metabolic system under tight control. The changes in insulin secretion and action are highly coordinated by the central nervous system (CNS) to ensure appropriate substrate switching between tissues to meet metabolic needs, such as in the postabsorptive to postprandial transition [2][3][4][5].

2. Physiology of Insulin Effects on Target Tissues

2.1. Liver

The liver plays a key role in glucose homeostasis. Its main metabolic function is to store glucose as glycogen after a meal and release it into the bloodstream (via glycogenolysis and gluconeogenesis) when required to maintain a constant concentration of glucose under any circumstances [6]. In hepatocytes, glucose transport does not depend on insulin. The high Km of GLUT2 glucose transporters (~20 mM) and glucokinase (~12 mM) allow glucose to enter the cells at a rate proportional to the concentration of extracellular glucose, facilitating glucose clearance following a meal [7][8]. Hepatic glucose production is inhibited by hyperinsulinemia and hyperglycemia [9][10].

Liver glycogen provides an immediately available reserve of glucose to maintain blood glucose concentrations, such as during hypoglycemia, fasting, or exercise [6][11][12]. Gluconeogenesis is a complex, branched pathway and occurs only in the liver and kidney cortex [13]. Control can be achieved by variations in the blood concentrations of the end product (glucose) and of the precursors by insulin and anti-insulin hormones and by central mechanisms involving the action of insulin at the hypothalamus and other parts of the brain [14][15][16][17][18]. The major precursors for liver gluconeogenesis are lactate, pyruvate, glycerol, and amino acids of which alanine and glutamine are quantitatively important [19].

A critical factor to consider in the regulation of the rate of gluconeogenesis is the supply of NEFA to the liver [20][21]. Increased rates of NEFA oxidation in hepatocytes activate key gluconeogenic enzymes and stimulate gluconeogenesis. Inhibition of lipolysis in the adipose tissue by insulin will therefore decrease the flow of both a stimulator (NEFA) and a substrate (glycerol) of gluconeogenesis to the liver, thus decreasing the rate of hepatic glucose production [20][21][22][23][24][25].

Glucagon and adrenaline mainly, but on a chronic basis also cortisol and growth hormone, compete with insulin and increase hepatic glucose production through an increase in glycogenolysis and gluconeogenesis [26][27][28][29]. Adrenaline, cortisol, and growth hormone also increase gluconeogenesis by an indirect mechanism, via an increase in lipolysis in adipose tissue and supply of glycerol and NEFA to the liver [30]. These effects of growth hormone and cortisol are of major importance in developing a transient insulin resistant state in the early morning hours during sleep, which helps to maintain euglycemia (see below).

2.2. Kidneys

The kidneys also express all the enzymes of the gluconeogenic pathway with the main gluconeogenic substrates being lactate, glutamine, and glycerol, whereas alanine is preferentially used by the liver rather than the kidneys [31]. Physiologic concentrations of insulin suppress renal gluconeogenesis and glucose production to approximately the same extent as in the liver, probably by intrarenal effects rather than by reducing substrate delivery [32][33][34]. Because NEFA have been shown to stimulate renal gluconeogenesis, the suppression of renal glucose production by insulin may be mediated, at least in part, by the decrease in adipose tissue lipolysis and plasma levels of NEFA when insulin concentrations are increased [33].

2.3. Skeletal Muscle and Adipose Tissue

Glucose transport is an important step in cell metabolism because it controls the rate of glucose utilization. In skeletal muscle and adipose tissue, the glucose transporter isoforms expressed are GLUT1, GLUT3, and GLUT4 [35]. In the postprandial state, insulin increases the rate of glucose transport mainly by stimulating the translocation of GLUT4 isoforms (Km ~5 mM) from the intracellular pool to the cell membrane [35][36]. In the fasting (basal) state, glucose transport is independent of insulin and is facilitated by the GLUT1 glucose transporters the low Km of which (~2 mM) is well suited for their function, to ensure basal glucose uptake [35].

Insulin increases the rate of glycolysis by increasing glucose transport and by regulating the activities of hexokinase and 6-phosphofructokinase [37][38][39][40]. Stimulation of glucose transport and the activities of these two enzymes by insulin, which leads to an enhanced rate of glycolysis, is of fundamental metabolic importance [2] for the following reasons: (a) when glycogen store in muscle is replete, the glucose taken up is converted to lactate, to maintain enhanced glucose utilization; (b) lactate produced and released by muscle (and adipose tissue) is taken up by the liver and converted to glycogen (known as the “indirect pathway” of glycogen synthesis) [41][42][43].

Lactate is produced by several tissues, but of these, only muscle and adipose tissue are sensitive to insulin and, therefore, subject to regulation [44][45]. The conversion of glucose to lactate in muscle and adipose tissue and the conversion to glucose in the liver represent a cyclic flow of carbon (Cori cycle) [46]. This can be described as an interorgan substrate cycle by analogy with intracellular substrate cycles [47]. It may have greater physiologic significance than just that of a carbon link between peripheral tissues (such as muscle and adipose tissue) and the liver. By maintaining a continuous flux, the Cori cycle provides a dynamic “buffer” of lactate in which its concentration remains relatively constant both in the tissues and the bloodstream [2]. The benefit of this is that it can be used by tissues whenever required for oxidation or for anabolic purposes [44][46].

Although skeletal muscle can store glucose as glycogen, in contrast to the liver, this tissue cannot release free glucose since it lacks the enzyme glucose 6-phosphatase. However, muscle can supply carbon for glucose production via the glucose-alanine cycle [48]. Alanine is a product of glycolysis in this tissue and is formed by adding an amino group from the metabolism of other amino acids, to pyruvate [49]. The transportation of alanine to the liver and its conversion to glucose via gluconeogenesis provides an effective mechanism to maintain blood glucose levels during fasting by using the large protein reserve in skeletal muscle [50].

Adipose tissue is more than just a passive repository for excess energy. Adipocytes secrete many hormones and cytokines which can affect energy homeostasis and the sensitivity of tissues to insulin [51]. Moreover, the processes of fat storage and mobilization are themselves regulated in a highly coordinated manner, with minute-to-minute control and rapid shifts in metabolic flux such as, for example, in the postabsorptive to postprandial transition [52][53]. The role of adipose tissue in buffering the level and flux of NEFA in the circulation in the fasting and postprandial period is crucial and has been considered analogous to the buffering of the level and flux of glucose by liver and muscle [54]. Adipose tissue provides its buffering action by regulation of the release of NEFA into the circulation according to the conditions of feeding or fasting through a change in the activity of the enzyme hormone-sensitive lipase (HSL) [55]. In addition, it also increases the rate of triglyceride clearance through an increase in the activity of the enzyme lipoprotein lipase (LPL) [56]. The activities of HSL and LPL are decreased and increased, respectively, by insulin [55][56].

The major store of triglycerides in the body is present in adipose tissue and it is mobilized in the form of NEFA and glycerol, which are then carried to other tissues via the bloodstream. Muscle can oxidize NEFA derived from adipose tissue and obtain energy. However, fatty acid oxidation in this tissue does more than provide energy. It provides a regulatory mechanism by which insulin and anti-insulin hormones can modify the rate and fate of glucose metabolism in muscle [2]. Thus, NEFA oxidation decreases the rates of glucose utilization and oxidation. In addition, glucose decreases the rate of NEFA oxidation, so that there is a reciprocal relationship between the oxidation of these two fuels; this control mechanism is known as the “glucose/fatty acid cycle” [57]. One principal point in this mechanism is that the pathway for fatty acid oxidation in muscle (β-oxidation and the Krebs cycle) depends upon the rate of lipolysis in adipose tissue and the ability of this tissue to control the blood concentrations of NEFA [58]. Evidence from human experiments has shown that it is not the increase in fat oxidation that inhibits indirectly insulin-stimulated glucose uptake, but instead, this abnormality results from accumulation of fatty acid metabolites in muscle cells, such as diacylglycerol and ceramides, which interfere with insulin signaling, thus leading to a failure of insulin to stimulate glucose transport [59][60].

Insulin inhibits adipose tissue HSL activity, thus decreasing the rate of mobilization of NEFA from adipose tissue, reducing blood levels of NEFA and leading to a greater rate of glucose utilization by muscle [20][21]. Given that muscle represents a large proportion of total body mass [61], insulin causes a substantial switch from fat to carbohydrate oxidation for the body’s tissues [62]. This is a more effective regulatory mechanism than that of glucose alone and illustrates the role in integrating fat and carbohydrate metabolism across tissues achieved by insulin signaling, permitting metabolism to adapt to changes in energy requirements under all circumstances [63].

Insulin affects vascular endothelium and increases muscle and adipose tissue blood flow by increasing vasodilatation and capillary recruitment [64][65][66]. Insulin-mediated increases in blood flow and insulin’s effects on tissue glucose uptake and metabolism are tightly coupled processes and, therefore, important determinants of tissue sensitivity to insulin [64][67]. In skeletal muscle, the increase in blood flow after a meal or during exercise increases the delivery of substrates for metabolism [63][68][69]. In the adipose tissue, the postprandial increases in the rates of blood flow by insulin are critical for the clearance of NEFA from the bloodstream, and hence facilitate insulin-stimulated glucose utilization in skeletal muscle [63][67][70].

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