Metabolism of Macro- and Micronutrients

Module 1.1

Metabolism of carbohydrates

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Learning Objectives

- To know major pathways of glucose metabolism in humans;
- To understand regulation of glucose metabolism in healthy subjects;
- To know effect of stress hormones on glucose metabolism;
- To be informed about alterations of glucose metabolism in sepsis and other illnesses.

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1. Carbohydrate in normal metabolism
2. Regulation of glucose metabolism
3. Metabolic responses to (critical) illness

Key Messages

- Glucose metabolism is primarily regulated by the balance between anabolic (insulin) and catabolic (epinephrine, nor-epinephrine, glucagon, cortisol and growth hormone) hormones;
- FFA (free fatty acids) are an important regulator of glucose metabolism;
- In fasting conditions FFA and catabolic hormones maintain glucose production and decrease glucose utilization in the insulin sensitive tissues (muscle and adipose tissue);
- In postprandial conditions, insulin stimulates glucose uptake, glucose oxidation and glucose storage in muscle. It stimulates fat storage in adipose tissue by stimulating glucose uptake. It inhibits glucose production;
- Physical stress, by increasing the secretion of catabolic hormones and FFA, causes insulin resistance and hyperglycaemia (the latter when increased insulin secretion can not compensate for insulin resistance). In addition, inflammatory mediators (TNF, interleukin 6 and others) are generally activated during critical illness and antagonize insulin’s actions (=induce also insulin resistance);
- Hyperglycaemia and insulin resistance may have deleterious effects on outcome in critical illness.
1. Carbohydrate in Normal Metabolism

1.1 Carbohydrate in Normal Metabolism
Plasma glucose levels are maintained normally within tight limits, which is particularly important in ensuring a steady supply of glucose to the brain. The concentration of glucose in plasma depends on the rate of entry of glucose in plasma and its uptake into the tissues. Under basal conditions these rates are equal and the plasma concentration is constant. Any change in plasma glucose is due to one rate (influx or efflux) exceeding the other. The rate of influx is dependent on the rate of production by liver, kidney or possibly gut under fasting conditions or the rate exogenous supply during nutrition (1,2). The rate of uptake is dependent on the mass effect of glucose (the height of the plasma glucose concentration) and on additional factors influencing uptake irrespective of a primary effect on plasma glucose concentration. Liver and muscle are the main tissues that regulate plasma glucose due to their large contribution to respectively production and uptake.

1.2 Glucose Production
Glucose-6-phosphatase is only expressed in liver, kidney and gut. This enzyme catalyzes the last enzymatic step common to glycogenolysis and gluconeogenesis, e.g. the hydrolysis of glucose-6-phosphate into glucose and inorganic phosphate. These organs are therefore the only organs to release glucose into plasma. The liver can produce glucose via glycogenolysis, while all 3 organs can synthesise glucose via gluconeogenesis. The main gluconeogenic substrates are lactate, glycerol and the gluconeogenic amino acids, especially alanine and glutamine. Alanine and lactate are the main gluconeogenic substrates for the liver. Glutamine, lactate and glycerol are the substrates of choice for the kidney (Fig. 1), while the gut prefers glutamine and glycerol as gluconeogenic substrates (2,3). As lactate carbon is derived from glucose, the conversion of lactate to glucose does not represent net glucose synthesis. Truly “new” glucose, therefore, is only derived from the breakdown of protein (amino acids) or fat (glycerol).

Figure 1 Substrates for gluconeogenesis
(Trends in Parasitology 2006; 22:410-415, with permission by Editor)

Tissue glucose uptake and metabolism
After an overnight fast, whole-body glucose utilization is equal to glucose production or ~2 mg/kg/min, equivalent to 200 gram/70 kg/day. Non-insulin dependent tissues account for ~70% of this disposal. The pattern of uptake is determined by the differential distribution of glucose transporter isoforms, that facilitate glucose transport, and on the glucose gradient between cytosol and interstitial fluid.

The transport of glucose across the cell membranes into muscle and fat cells is the rate-limiting step of glucose utilization in humans. Glucose cannot diffuse across the cell membrane and must be carried into the interior of the cell by specialized proteins, called glucose transporters (Glut). Six glucose transporters have been described. For this review Glut 1 and Glut 4 are the most important. Glut 1 is very widely distributed throughout the tissues and probably mediates basal glucose transport. Glut 4 is expressed in insulin-sensitive tissues. Glut 4 is regulated by insulin, which has
little influence on the other Glut proteins. Unlike the other Glut’s, that lie in the cell membrane, Glut 4 is normally located in vesicles in the cytoplasm. Insulin recruits these vesicles to be translocated to the cell membrane, with which they fuse. The intramembrane Glut 4 is then able to function as pore to facilitate glucose uptake. Insulin may also enhance the activity of individual Glut 4 units. Via this mechanism, insulin can stimulate glucose uptake several-fold in the insulin-sensitive tissues, muscle and fat. Uptake via the other Glut’s is by mass action. The higher the plasma glucose concentration the more glucose is taken up via these transporters, provided that glucose is metabolized and low concentrations of glucose are maintained intracellularly. This process is also regulated as excessive glucose uptake will lead to accumulation of glucose-6-phosphate, which will in turn inhibits hexokinase, that catalyses the formation of glucose-6-phosphate from glucose; intracellular glucose will rise and the rate of glucose entry will fall (4). After uptake into the cell, glucose has to be metabolized. Two pathways are possible: glycolysis, with subsequent oxidation and formation of lactate, or storage as glycogen. Theoretically, de-novo lipogenesis, the formation of fat from glucose, is also a possibility, but measurements in humans have shown that this pathway is of minor quantitative importance under eucaloric circumstances (5). Insulin not only stimulates glucose uptake, but also stimulates the enzymes of both pathways with concomitant stimulation of storage. Glucose oxidation is only stimulated to the degree that fat oxidation is reduced by the inhibitory effects of insulin on lipolysis and the concomitant reduction of free fatty acid supply.

2. Regulation of Glucose Metabolism

2.1 Regulation of Glucose Metabolism in Healthy Subjects
(for extensive discussion see ref 6)

2.1.1 Insulin
Insulin has a central role in the regulation of carbohydrate metabolism. It inhibits glucose production by liver and kidney and stimulates peripheral glucose disposal. In healthy subjects, a consistent relationship is found between plasma insulin concentration and its effect on glucose metabolism. In its regulation of plasma glucose concentration the primary influence is inhibition of glucose production, while higher insulin concentrations are needed for stimulation of glucose uptake (fig 2).

![Figure 2 The relation between plasma insulin concentration and the rates of glucose production and glucose uptake](image)
2.1.2 Glucagon

Glucagon stimulates hepatic glycogenolysis and gluconeogenesis. It stimulates glycogenolysis by activation of glycogen phosphorylase, the rate-limiting enzyme for glycogenolysis in the liver. Glucagon stimulates gluconeogenesis by stimulating the conversion of fructose-1,6 biphosphate to fructose 6-phosphate. In addition, it increases the gene transcription of PEPCK (phosphoenolpyruvate carboxykinase), a key enzyme in gluconeogenesis. The gluconeogenic effect of this hormone is brought about solely by its hepatic action because glucagon does not increase peripheral release of any of the major gluconeogenic substrates.

Glucagon infusion in humans only transiently stimulates glycogenolysis, in contrast to its sustained stimulation of gluconeogenesis. Administration of an inhibitor of glycogenolysis decreases glucagon-stimulated glycogenolysis but causes no change in total glucose production as a result of a reciprocal increase in gluconeogenesis. From these and other studies, the existence of reciprocity between glycogenolysis and gluconeogenesis has been postulated. Alternatively, there could be another inhibitory feedback system within the liver maintaining total glucose output at a certain level. Therefore, contrary to frequent citations in the literature, stimulation of gluconeogenesis cannot be considered to be synonymous with stimulation of total glucose production.

2.1.3 Catecholamines

Catecholamines stimulate glycogenolysis and gluconeogenesis. Part of the stimulatory response is caused by stimulation of glucagon secretion and part of it is caused by stimulation of certain enzymes in the glucose pathway (pyruvate carboxylase). Like glucagon infusion, epinephrine only stimulates glycogenolysis transiently, in contrast to its sustained stimulation of gluconeogenesis. Like epinephrine, norepinephrine also causes only a transient stimulation of glycogenolysis, in contrast to its sustained stimulation of gluconeogenesis. Both catecholamines decrease glucose clearance, but their effect on production of glucose is much greater compared to their effect on disposal (7). Catecholamines also decrease glucose uptake. Therefore they increase plasma glucose concentration via a dual action on production and disposal of glucose.

In man catecholamines do not usually play an important role in maintaining plasma glucose concentration during fasting. However, enhanced secretion of catecholamines compensates and prevents hypoglycaemia, when glucagon secretion is deficient (eg in long-standing type 1 diabetes).

2.1.4 Cortisol

During progressive fasting, serum cortisol increases as a result of an increase in secretion. Corticosteroids are known to activate gluconeogenic enzymes, to stimulate the uptake of (gluconeogenic) amino acids in the liver, augment transfer of amino acids from muscle to liver and to induce insulin resistance. Short-term hypercortisolism in healthy individuals with normal beta-cell function decreases insulin action but does not alter rates of glucose production and gluconeogenesis. In addition, cortisol impairs the ability to suppress glucose production, which due to accumulation of glucose in the glucose space results in impaired peripheral glucose clearance (8). In contrast to the acute effects of glucagon and catecholamines, the effect of cortisol takes several hours to develop.

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2.1.5 Growth Hormone

Like cortisol, growth hormone may induce resistance to insulin action on glucose production and glucose disposal by altering substrate availability and promoting enzyme induction. Progressive starvation enhances growth hormone secretion. Like cortisol the effect of growth hormone on glucose metabolism takes several hours to develop.

2.1.6 Free Fatty Acids (FFA)

In short term starvation, coordinated action is needed to limit unrestrained glucose disposal, and, consequently, to maintain brain function by preventing hypoglycaemia. During fasting, a series of metabolic adaptations are also essential to guarantee sufficient energy production. These changes therefore include a decrease in the rate of glucose production and in plasma glucose concentration by ~25% after 72 hours of fasting, concomitant with a doubling of lipolysis. They are also accompanied by a ~50% decrease in insulin stimulated glucose disposal. “Acute” elevation of plasma FFA levels is a major factor co-ordinating fasting-induced insulin resistance. It is now well
established that this FFA-induced insulin resistance: (a) occurs mostly in muscle which accounts for > 80% of insulin-stimulated glucose uptake (b) develops between 2 and 6 hours after elevation of plasma FFA levels, (c) disappears ~4 h after FFA levels have returned to normal and (d) is dose dependent.

3. Metabolic Responses to (Critical) Illness

3.1 Insulin Action and Insulin Resistance

Insulin resistance can be defined as a state in which a given concentration of insulin elicits a suboptimal biological response (Fig. 3). Although insulin’s effects are pleiotropic, insulin resistance usually refers to impairment of the action of insulin on glucose homeostasis. Insulin inhibits glucose production and stimulates glucose uptake, oxidation and glycogen synthesis in the insulin sensitive tissues, muscle and adipose tissue. Suppression of production and stimulation of oxidation of glucose require less insulin than stimulation of uptake. In the traditionally glucocentric view of insulin resistance a defect in insulin action requires more insulin than usual to maintain normal glucose fluxes. This glucocentric view ignores the fact that insulin has many more regulatory tasks than those related to glucose metabolism. One of these other important tasks of insulin is suppression of lipolysis. Less insulin is required to suppress lipolysis (suppression of free fatty acid (FFA) flux) than for regulation of glucose metabolism. Numerous data have shown that lipids and especially high FFA levels will induce insulin resistance and there is a growing appreciation that chronic elevation of FFA levels is an early event in the development of insulin resistance. Insulin resistance, in turn, will further increases FFA levels, creating a vicious cycle, further worsening insulin resistance. In this way, although insulin resistance can worsen the metabolic abnormalities, it is never the primary contributor. However, insulin resistance may be a patchy defect, as there are situations in which other actions of insulin are normal, despite abnormal insulin-mediated glucose handling and vice versa.

Most of our current understanding of the mechanisms of insulin resistance has evolved from studies using the euglycemic hyperinsulinemic clamp technique. This is frequently referred to as the golden standard in the measurement of insulin sensitivity. It is a conceptually simple technique, although technically somewhat more complex. It is performed by infusing insulin at a constant rate to achieve the desired plasma insulin level. Plasma glucose is monitored every 5 minutes and glucose is infused at variable rates to maintain euglycemia. Any plasma glucose concentration can be chosen, but studies at euglycemia are preferred to eliminate the mass effect of glucose on its uptake. When the rate of glucose infusion has stabilized (after 2-3 hr) glucose turnover (the sum of remaining endogenous production plus exogenous infusion) can be measured with isotopes and the data can be compared to those obtained in a control group with the same plasma insulin level. Isotope studies are not necessary when such a high plasma insulin concentration is chosen that complete suppression can be expected.

Studies in healthy humans have shown that skeletal muscle is the principal site of glucose uptake under insulin-stimulated circumstances, accounting for approximately 75% of glucose disposal after glucose infusion. These studies have also shown that lipolysis is the most insulin-sensitive process followed by glucose production and, far behind, glucose uptake with EC50 values in the physiological range only for insulin-induced inhibition of lipolysis and glucose production, but not for insulin-stimulated glucose uptake.

Insulin resistance in diabetes mellitus is both inherited and acquired due to life style eg overeating, obesity and physical inactivity. In disease related insulin resistance, weight gain and inactivity can have a role, but disease induced secretion of the gluco-counter regulatory hormones, cytokines and FFA (free fatty acids) are probably more important contributing factors. Despite intensive research efforts, there is, so far, no clear understanding of all the factors causing insulin resistance either in diabetes mellitus or in disease induced insulin resistance (9-11).
3.2 Glucose Metabolism in Acute and Chronic Disease

It has been known since the time of Claude Bernard that injury and other illnesses can cause hyperglycemia, and that hyperglycemia is a frequent but not invariable finding in sepsis and other critical illnesses under basal circumstances. Hyperglycemia can be caused by an increase in glucose production, a decrease in glucose tissue uptake, or a combination of both. There is a direct relationship between the severity of the disease and the degree of stimulation of glucose production. Diseases like liver cirrhosis, AIDS without concomitant infection and hyperthyroidism hardly stimulate glucose production at all, while impressive increases of up to 250% of the normal production rate are found in metastatic cancer, severe pancreatitis, sepsis and burns. Despite this increase, endogenous glucose production can sometimes, but not invariably, be easily suppressible with only slightly higher insulin concentrations than those necessary for suppression in healthy subjects, suggesting that a high rate of glucose production can be found despite moderate insulin resistance at the hepatic level eg in sepsis.

In the basal state, glucose uptake is mainly insulin-independent. In healthy subjects, after an overnight fast, ~80% of basal glucose tissue uptake is insulin-independent and 20% insulin-dependent. In insulin-stimulated circumstances, major defects in glucose tissue uptake can be found, although not invariably. The maximal physiological effectiveness of insulin is not markedly reduced in severe trauma and injury. In contrast, in sepsis the maximal effectiveness of insulin is decreased 50% below normal. Comparable defects are also found in diseases without fever, as in well-nourished patients with stable liver cirrhosis.

Glucose is either oxidized or stored after uptake. An impairment in glucose uptake is not necessarily followed by an impairment in both intracellular pathways. Undisturbed glucose oxidation, but major defects in glucose storage characterize sepsis and liver cirrhosis. In other diseases, like sepsis, cancer or pancreatitis, glucose oxidation is also inhibited.

In conclusion: in acute and chronic disease major defects in glucose metabolism can be found sometimes under basal conditions but more often in insulin-stimulated circumstances. Defects in insulin action, if present, do not necessarily involve the different metabolic pathways of glucose to the same degree.
3.3. Mediators in the Metabolic Responses to (Critical) Illness

Orchestrated “counterregulatory” hormonal responses, cytokine release, and signals from the nervous system, all affecting glucose metabolic pathways, bring about the so-called diabetes of injury. The hormones involved include catecholamines, cortisol, glucagon, and growth hormone. Proinflammatory cytokines affect glucose homeostasis indirectly, by stimulating counterregulatory hormone secretion, and directly, by altering insulin receptor signaling. Furthermore, both endogenous and exogenous catecholamines promptly inhibit insulin secretion from β cells, a phenomenon mainly observed in the acute phase of injury when catecholamine secretion is maximal. However, little is known about the exact molecular basis of the insulin resistance which develops subsequently in critically ill patients and may last for days or weeks, depending on the severity of injury and its complications. The diabetes of injury used to be interpreted as an adaptive stress response and as such important for survival. Particularly, the overall increase in glucose turnover and the fact that hyperglycemia persists despite abundantly released insulin were considered arguments in favor of tolerating moderately elevated blood glucose levels during critical illness. Indeed, if one considers the hyperglycemia of injury as beneficial in promoting cellular glucose uptake in non-insulin-dependent tissues, including damaged and granulating tissue, modest degrees of hyperglycemia were considered as possibly beneficial. Consequently, blood glucose concentrations of 8-12 mmol/l were recommended to maximize cellular glucose uptake while avoiding hyperosmolality. In addition, moderate hyperglycemia was often viewed as a buffer against hypoglycemia-induced brain damage. In 2001, however, the critical care community was forced to reconsider this dogma, as a large, randomized, controlled, clinical study in surgical patients showed that preventing even moderate hyperglycemia during critical illness substantially improved outcome (9). Many mechanisms have been put forward to explain this favorable result, but none of them are proven. The exact molecular basis for the increased susceptibility for these toxic effects in the critically ill patient remains to be explored (12). The setting in which induction of euglycemia is induced is also important, as a comparable study in critically ill medical patients could not repeat the very favorable results obtained in surgical patients (13).

Summary

This module describes regulation of glucose metabolism in health and (critical) illness with emphasis on the role of insulin, glucoregulatory hormones and free fatty acids. The importance of maintenance of euglycemia is touched on.

References