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EDUCATIONAL PAPER

Basics in clinical nutrition: Carbohydrate metabolism

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Carbohydrate;
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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 and stress hormones on glucose metabolism.
—To be informed about alterations of glucose metabolism in sepsis and aggression.

Carbohydrate in normal metabolism

Dietary carbohydrates usually provide between 40 and 70% (currently recommended 50—55%) of our total daily energy intake. Of ingested carbohydrates, the major portion is represented by starch and a minor (recommended less than 20%) portion by dissaccharides (mostly sucrose and lactose) and monosaccharides. Dietary carbohydrates are digested to hexoses by the sequential actions of amylases and isoamylases in the gut and disaccharidases in the brush border of enterocytes, and are absorbed in the portal circulation as hexoses (>90% as glucose when dietary intakes follow current recommendations).

Glucose is a main source of readily available energy for virtually all cells of the body. It also takes part in various biosynthetic processes (synthesis of protein and fatty acids, glycosylation, etc.), although this represents a very minor portion of its overall metabolism. Blood glucose is maintained, during fasting at a concentration of 0.8—1.2 g/l (4.4—6.7 mmol/l). Given the fact that glucose diffuses freely in extracellular water (volume approximately 0.2 times body weight), this represents about 14 g in a 70 kg male individual. Except for this small amount of extracellular glucose, there are approximately 70—120 g CHO stored as glycogen in the liver and 200—1000 g in skeletal muscle. The use of the latter is however restricted to skeletal muscle since muscle cannot release glucose into the circulation due to lack of the enzyme glucose-6-phosphatase.

Regulation of glucose metabolism

Glucose (and other macronutrients) metabolism is primarily regulated by hormones, with the contribution of

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Table 1 Effects of hormones on whole body glucose metabolism[8]

	Insulin	Glucagon	Cortisol	Adrenaline	Growth hormone
Glycogenolysis	↓↓	↑↑		↑↑	
Gluconeogenesis	↓	↑	↑↑	↑	↑
Muscle/adipose glucose uptake	↑↑		↓	↓	↓
Glycogen storage	↑	↓	↑	↓	↓
Glucose oxidation	↑		↓	↓	↓

neural and local factors. Insulin is the main anabolic hormone: its secretion remains relatively low between meals, and this basal secretion essentially regulates hepatic glucose production. Basal (fasting) glucose production is a major determinant of fasting glycaemia (Table 1). Insulin secretion increases after a carbohydrate meal, and the hyperinsulinemia, which ensues glucose utilization and storage.

Organs and tissues can be classified as:

—*insulin-sensitive*: in such tissues, as skeletal muscle and adipose tissue, insulin acutely promotes glucose uptake by stimulating the translocation of specific glucose transporters, GLUT4 to the plasma membrane; these insulin-sensitive tissues use glucose after carbohydrate ingestion, and lipids between meals;
—*insulin-insensitive*: in these tissues, glucose uptake is not dependent on insulin concentration, and glucose transport and oxidation remain fairly constant during the day due to the presence of low Km glucose transporters (GLUT1, GLUT3) and hexokinase. The brain is noninsulin-sensitive, and uses about 1 mg/kg/min glucose (about 1.5 g/kg/day) throughout the day.[8]

A group of catabolic hormones, whose major representatives are glucagon, adrenaline, cortisol, and growth hormone, opposes insulin's actions. Secretion of these hormones increases between meals or during stress or aggression. As a whole, they decrease glucose uptake in insulin-sensitive tissues and stimulate hepatic glucose production. More than by a single hormone, glucose metabolism is regulated by the balance between insulin and catabolic hormones (Fig. 1).

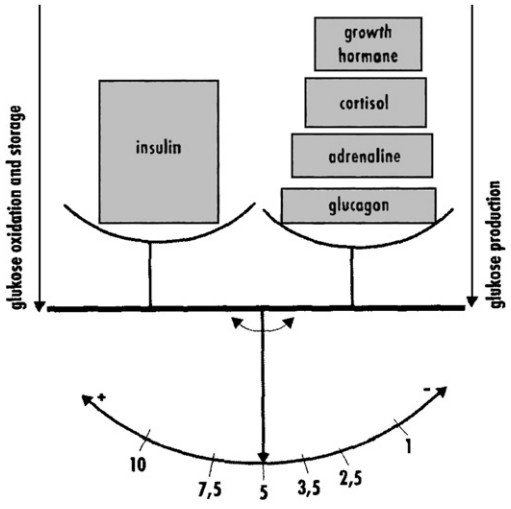

Figure 1 Regulation of glycaemia by anabolic (insulin) and catabolic (glucagon, adrenaline, cortisol, growth hormone) hormones.

In postabsorptive conditions, secretion of glucagon, cortisol, adrenaline and growth hormone is relatively high, and insulin secretion is low. Portal insulin concentrations are higher than systemic, and insulin limits the stimulation of glucose production by catabolic hormones, allowing a match between glucose production and glucose utilization in noninsulin-sensitive tissues (Fig. 2). After ingestion of a carbohydrate meal (Fig. 3), insulin secretion increases and that of catabolic hormones decreases, resulting in inhibition of hepatic glucose production and stimulation of glucose utilization in insulin-sensitive tissues. High portal glucose and insulin concentrations also promote net hepatic glucose uptake and hepatic glycogen storage.[4]

Effects of stress on glucose metabolism

Stress responses have evolved to allow the organism to face potentially dangerous conditions, such as the encounter with a predator. It has as its hallmarks an enhanced secretion of catabolic hormones and a stimulation of the sympathetic nervous system. Sympathetic stimulation and adrenaline increase cardiac output and decrease blood flow to splanchnic organs. Paradoxically, sympathetic stimulation during acute stress can produce muscle vasodilation, which redirects blood flow to skeletal muscle. Simultaneously, catabolic hormones (essentially glucagon and adrenaline in acute settings) increase glycogen degradation and glucose production and decrease glucose utilization in insulin-sensitive tissue. Growth hormone decreases insulin's actions and stimulates lipolysis. The increased plasma free fatty acid concentration stimulates lipid oxidation and favors gluconeogenesis in liver cells. During more prolonged stress, high cortisol levels promote gluconeogenesis and inhibit glucose uptake in insulin-sensitive tissues. Cortisol stimulates not only gluconeogenesis and hepatic glucose output, but also hepatic glycogen synthesis, thus allowing maintenance of some ''reserve'' of carbohydrate in the liver. The major effects of catabolic hormones on glucose metabolism are shown in Tables 1 and 2. Overall, the acute stress or 'fight or flight' responses allow the body to maintain an ample oxygen and substrate supply to the brain and skeletal muscle (at the expense of splanchnic organs) and to spare glucose for the brain. This allows optimal muscle activity for flight or fight.

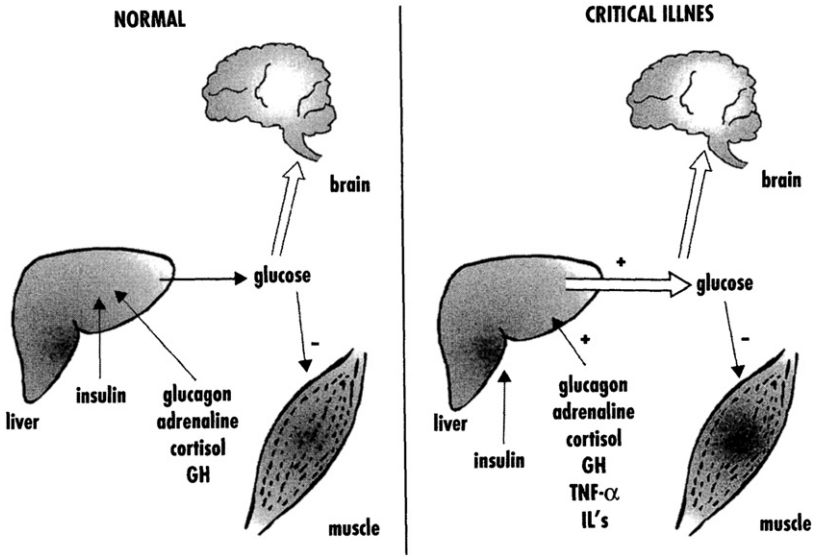

Figure 2 Regulation of fasting glucose production and fasting glycaemia in normal conditions (left) and critical illness (right).

Metabolic responses to critical illness

Critical illness (sepsis, trauma, etc.) elicits responses, which are, in several aspects, similar to acute stress. Secretion of catabolic hormones increases and stimulates endogenous glucose production while decreasing insulin's actions on insulin-sensitive tissues. In contrast to the encounter with a predator, these responses are longer lasting due to the duration of the disease process, allowing ample time for cortisol to produce its actions. Increases in plasma adrenaline and glucagon acutely stimulate glycogenolysis and increase hepatic glucose output. High cortisol levels stimulate muscle and splanchnic protein catabolism, increase hepatic gluconeogenesis, and decrease muscle glucose uptake. This produces a state of hyperglycemia together with insulin resistance and hyperinsulinaemia.

Critical illness is generally associated with some degree of tissue damage and/or infection. Under such circumstances, immune cells and macrophages secrete inflammatory mediators such as TNFα and interleukins (IL's). TNFα has several major effects on glucose metabolism. High levels of TNFα increase glucose turnover in the fasting state, but produce insulin resistance during hyperinsulinaemia. IL_1, IL_2 and IL_6 also contribute to reduce insulin sensitivity during inflammation.[5]

As a consequence of these prolonged secretions of catabolic hormones and of inflammatory cytokines, critically ill patients have increased fasting plasma glucose and insulin due to high hepatic glucose production and insulin resistance (Table 1 and Fig. 3). Furthermore, glucose production is not suppressed during carbohydrate administration, and stimulation of glucose uptake is impaired, resulting in postprandial hyperglycemia (Table 2. and

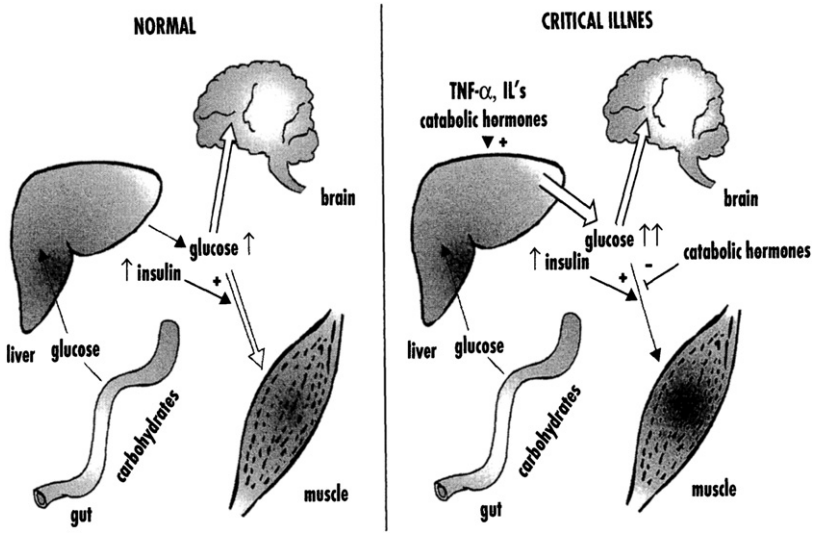

Figure 3 Regulation of postprandial glucose metabolism in normal conditions (left) and critical illness (right).

Table 2 Endogenous (hepatic) glucose production ($g\,kg^{-1}\,day^{-1}$)

	Healthy subjects	Critically ill patients
Overnight fast	~2.5—3	3.5—10
Long fast	~1.5	3.5—10
Postprandial	~0.5—1	1.5—10

Fig. 3). Alterations in glucose metabolism occur in parallel with increased endogenous protein breakdown, which provide gluconeogenic substrates to the liver. Although these metabolic responses may be favorable in the short term by allowing mobilization of endogenous glucose for the brain and inflammatory tissues, they will in the long term lead to enhanced proteolysis, loss of lean body mass, and organ dysfunctions. Furthermore, high plasma glucose concentrations in critically ill patients appear to be associated with poor clinical outcome through mechanisms, which remain presently unknown, although increased infection risk appears to be an important factor.[10]

Summary

Glucose metabolism is primarily regulated by the balance between anabolic (insulin) and catabolic (epinephrine, glucagon, cortisol, growth hormone) hormones. In fasting conditions, catabolic hormones enhance hepatic glucose production and decrease glucose utilization in skeletal muscle and adipose tissue. In postprandial conditions, insulin stimulates glucose oxidation in skeletal muscle and glucose storage in liver and skeletal muscle and inhibits hepatic glucose production. Stress, by increasing catabolic hormones, causes insulin resistance and hyperglycemia. In addition, inflammatory mediators (TNFα, interleukins) are generally activated during critical illness and antagonize insulin's actions. This results in marked insulin resistance and hyperglycemia, which may have deleterious effects in the long term.

Conflict of interest

The author has no conflict of interest to declare.

Further reading

1. Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg* 1984;**200**:264.
2. Cherrington AD. Control of glucose uptake and release by the liver in vivo. *Diabetes* 1999;**48**:1198.
3. Frayn KN. *Metabolic regulation*. London: Portland Press; 1996.
4. Gerich JE. Control of glycaemia. *Baillieres Clin Endocrinol Metab* 1993;**7**:551.
5. Grimble RF. Inflammatory status and insulin resistance. *Curr Opin Clin Nutr Metab Care* 2002;**5**:551.
6. McEwen BS. Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. *Metabolism* 2003;**52**:10.
7. Newsholme EA, Leech AR. *Biochemistry for the medical sciences*. Chichester: John Wiley & Sons; 1983.
8. Tappy L. Regulation of hepatic glucose production in healthy subjects and in NIDDM. *Diabete Metab* 1995;**21**:233.
9. Thorens B. Glucose transporters in the regulation of intestinal, renal, and liver glucose fluxes. *Am J Physiol* 1996;**270**:G541.
10. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;**345**:1359.
11. Wilmore DW, Robinson MK. Metabolism and nutritional support. In: Fischer JE, Holmes CR, editors. *Surgical basic science*. St-Louis: Mosby-Year Book; 1993. p. 125.