Hormonal control of metabolism: regulation of plasma glucose

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Abstract

The control of plasma glucose needs to be tightly monitored because hyperglycaemia and hypoglycaemia can lead to severe clinical problems, including death. In this article the major mechanism for the transport of glucose into and out of the blood and how that mechanism is used to monitor the circulating concentrations of glucose are discussed. A number of hormones regulate glucose in response to changes in plasma concentrations. Insulin promotes the removal of glucose and its conversion to glycogen. Glucagon, in response to falling glucose concentrations, increases the breakdown of glycogen and the release of glucose from the liver. There are many other hormones that play a part in assisting the functions of insulin and glucagon. Failures in the appropriate production of such hormones may lead to the unregulated changes in plasma glucose and subsequent health problems.

Keywords

Glucose Plasma Homeostasis

Hormonal Regulation

The concentration, and hence the supply, of glucose in the blood must be maintained within acceptable levels. For example, the brain, which has a very large demand for glucose (120 g/day) would suffer adverse effects (functional impairments, coma and even death) if there was a decrease in plasma glucose to below 4.0 mmol/litre. Hyperglycaemia, sustained elevation of fasting plasma glucose above 7 mmol/litre, may result in organ damage or ketosis in chronic or acute cases, respectively. Plasma glucose comes from the dietary intake of sugars and endogenous production in the liver and kidney. There can also be a rise in plasma glucose when some tissues reduce their uptake; some tissues achieve this by producing glucose for their own consumption, although this is a minor mechanism predominantly effective in starvation. Glucose is the primary source of energy for most tissues; therefore there is a constant drain of glucose from the blood. A balance between supply and demand must be maintained to prevent the complications mentioned above, but more importantly to keep the body functioning as a whole.

Plasma glucose is monitored by a range of mechanisms in the body and regulated by several hormones. The body must be able to respond to significant increases in plasma glucose, such as after a carbohydrate-rich meal, or decreases, such as during fasting. The body must also be able to react quickly to demands on the energy supply chain during exercise or survival responses (e.g. the fight or flight response).

The fate of glucose within particular cells is also dependent on the action of hormones regulating the metabolic pathways. As discussed below, the interplay between the metabolism of glucose and the circulating glucose is regulated largely by the same hormones. For example, insulin, secreted in response to a rise in blood glucose, effects an increased transport of glucose into cells. At the same time, insulin promotes the conversion of glucose to glycogen (the major storage form of glucose) and reduces the activity of other pathways that may lead to the production of glucose (gluconeogenesis) from other metabolites. The result is a net decrease in plasma glucose. Conversely, glucagon, produced in response to a decrease in plasma glucose, promotes the breakdown of glycogen, which in the liver can be exported to the blood as free glucose. At the same time the metabolic pathways that use glucose are inhibited to reduce the demand for glucose.

Transport of glucose

Glucose molecules cannot cross the plasma membrane because of the hydrophobic nature of the membrane. Transport across the membrane is facilitated by a number of transporter molecules expressed on the surface of cells. These molecules have been given the acronym GLUT (glucose transporters). There are multiple isoforms, some of which are expressed on different cell types. How they operate and their responsiveness to the regulatory hormones is key to understanding how glucose is removed from the blood. GLUT-1 is a constitutive (i.e. unresponsive to hormone action) transporter of glucose and is responsible for the supply of a basal level of glucose. It is found in a number of cell types including the brain and the endothelial cells of the blood brain barrier; important as the brain is largely dependent on glucose as a primary energy source. GLUT-1 also has an important function in the transport of glucose across epithelial layers, for example, from the blood stream across the capillary to the target tissue. GLUT-2, found in liver and kidney cells (but not solely), is important because it not only absorbs glucose but can also transport glucose into the blood when plasma concentrations are low. A second important class of transporters is the sodium-

dependent glucose co-transporters (sGLTs). sGLT1, found within the cells of the intestine, is the major facilitator for the uptake of glucose from dietary sources. Unlike the GLUT transporters that mediate facilitated diffusion of glucose down its concentration gradient into cells, sGLT1 is a key component of the secondary active transport of glucose from the lumen of the gut against its concentration gradient into the intestinal cells. This movement of glucose against its concentration gradient by sGLT1 is achieved by the co-transport of sodium down its electrochemical gradient, which in turn is maintained by the use of metabolic energy by Na-K ATPase. Within the kidney sGLT2, found within the proximal tubule of the nephron of the kidney is important in glucose reabsorption.

Some GLUT molecules are responsive to hormonal action. GLUT-4, found in adipose and skeletal tissues, is expressed at low levels on cell surfaces when glucose is not readily available. In the presence of high concentrations of insulin, as a result of a rise in blood glucose, cell signaling events induce an increase in cell surface expression of GLUT-4, with the effect of increasing the uptake of glucose from the blood.

Physiological monitoring of blood glucose

GLUT-2 serves an important function in monitoring plasma glucose, particularly in protecting the body from hypoglycaemia. GLUT-2 is found in α- (glucagon-secreting) and β- (insulin-secreting) cells of the pancreas and in glial cells in the CNS. It is a high-affinity receptor for glucose and, as such, is very sensitive to glucose concentrations. Loss of GLUT-2 in animal models can be lethal because there is a resulting inability to manage low plasma glucose. Auto-antibodies to GLUT-2 have been found in patients with type 1 diabetes, suggesting a role for the loss of this sensor in the development of the disease.[1] It is not entirely clear how GLUT-2 responds to low concentrations, but there is probably more than one mechanism. The most likely mechanism is the glucose-sensing ability of β cells. When plasma (and interstitial) glucose is high GLUT-2 transports the glucose into β cells. The rise in glucose and/or metabolites derived from glycolysis within β cells triggers the production of insulin.[2] Conversely, the influx of glucose into the α cells triggers a signalling event that results in the inhibition of glucagon production. However, glucagon secretion still Increases to prevent the decrease In hepatic glucose output and hypoglycaemia that may occur if the increase in the insulin:glucagon ratio was to continue unchecked. The molar ratio of insulin:glucagon is usually around 2.0. Increases In this ratio (e.g., after a meal) enhances glucose uptake, utilisation and conversion to glycogen; whereas decreases in the ratio (due to either increased insulin or decreased glucagon; seen during fasting and prolonged exercise) leads to increased glycogenolysis, gluconeogenesis, and amino acid mobilisation; thereby maintaining a supply of glucose to the CNS. A fine balance between insulin and glucagon levels is achieved, notably by a form of self regulation. Production of glucagon is regulated by plasma levels of insulin and it has been observed that intra-islet insulin action is essential for suppression of glucagon in response to hyperglycemia, that is, glucagon is not repressed solely by high glucose levels. In addition, GABA (γ-aminobutyric acid) produced in β cells also affects glucagon secretion. While there is no apparent rise in GABA levels as a result of hyperglycaemia, insulin appears to upregulate the GABA receptor on α cells, inhibiting formation of glucagon.

The brain also has a part to play in the sensing of blood glucose via GLUT-2 expressed on glial cells. The pancreatic α cells are also under the control of the sympathoadrenal response and epinephrine is secreted after a fall in glucose, prompting a subsequent increase in glucagon levels. The classical "fight or flight" response reflects the role of neurotransmitters such as GABA or acetylcholine evoking epinephrine production. The α cells also respond to a reduction in insulin levels, whereby low concentrations trigger the production of glucagon. Thus, there is a reciprocal monitoring of blood glucose by GLUT-2, where the actual response is dependent on the cell type. It is worth noting that there may be a redundancy in monitoring via GLUT-2, as GLUT-1 in animal models can functionally replace GLUT-2.

Hormonal prevention of hyperglycaemia

Hyperglycaemia is a major problem, and various hormones are mobilized to reduce excess blood glucose (Table 1). Whilst insulin is a major factor in controlling plasma glucose concentrations, other hormones also have important roles. Insulin is produced from a prohormone (proinsulin) that is cleaved into two components: insulin and C-peptide. The ability of insulin to decrease plasma glucose is well understood, but the functionality of C-peptide is only beginning to become clear. C-peptide can be shown to increase the effectiveness of insulin-dependent uptake, suggesting that it has a role in carbohydrate metabolism.

After a carbohydrate-containing meal, various gut hormones, termed incretins, are released into the blood as a first-line of defense against hyperglycaemia. The incretins have a stimulatory effect on the production of insulin, and it seems that glucose in the lumen of the gut stimulates release of two incretins, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1), which possibly act as a forewarning to the pancreatic β cells to begin producing insulin, and act by reducing glucagon production from α cells.[3] Experimentally, these actions explain why oral glucose can be more effective in stimulating insulin release because intravenous glucose bypasses this mechanism. However, it is important that control of incretin secretion is maintained to prevent hypoglycaemia. Recently, two drugs (exenatide and sitagliptin), based on the action of incretins, have been made available for the treatment of type 2 diabetes because a number of individuals with this disorder have shown a decreased functionality of the incretins.

Circulating insulin promotes uptake of plasma glucose primarily by inducing the increased surface expression of the GLUT-4 receptor on a number of tissues. Skeletal muscle tissue is the most important repository for glucose in the fed state, and its sensitivity to insulin is important for maintaining glycaemic homeostasis. During exercise the muscle can become more sensitized to the effect of insulin, inducing increased glucose uptake and post-exercise conversion to glycogen;[4] however, the enhancement is not insulin dependent and occurs due to a currently undefined mechanism.

Other hormones have the potential to reduce the occurrence of hyperglycaemia. Insulin-like growth factor 1 (IGF-1) is produced by a number of tissues in response to growth hormone and is structurally similar to insulin. It can replace insulin, although with reduced activity, and clinical trials investigating its effect in type 1 and 2 diabetes are ongoing. IGF-1 may bind to the insulin receptor, thus activating the insulin-responsive signaling pathway. Leptin, a hormone released by adipose tissue acts to suppress appetite and hence sugar intake. The receptor for this hormone is found in the hypothalamus, notably in the ventral medial nucleus (the so-called satiety centre). Leptin can

exert direct effects on glucose and lipid metabolism in peripheral tissues. In peripheral tissues leptin inhibits lipogenesis, glycogen synthesis, stimulates utilization of fatty acids, leading to decreased triglyceride content, and causes an improvement in insulin sensitivity. Leptin may function as a whole-body energy store indicator because fasting can decrease leptin concentrations.

The effect of insulin within the cell is important in the regulation of plasma glucose. In a cell, glucose is 'trapped' by rapid conversion to glucose-6-phosphate (G6P); the fate of glucose is either to enter the glycolytic pathway as a perquisite to energy production via oxidative phosphorylation within the mitochondria or anaerobically by conversion to lactate. Alternatively G6P can be converted to glycogen for storage for later usage as an energy source. In the liver and kidney, the two major gluconeogenic organs, G6P can be converted back to glucose and exported in the blood; other tissues lack the appropriate enzyme, glucose-6-phosphatase (G6Pase). If the energy status of the cell is high, as evidenced by high levels of ATP or of various metabolites of the energy pathways, various feedback mechanisms come into play to halt glycolysis and there is a need to route the excess glucose into glycogen. The binding of insulin to its receptor induces a signaling cascade, which halts the conversion of glycogen to glucose, while simultaneously promoting the production of glycogen by enhancing the activity of glycogen synthase and inhibiting the glycogen catabolic enzyme glycogen phosphorylase; high levels of G6P within the cell also enhance the activity of the synthase. At the same time the signaling cascade prevents gluconeogenesis from non-carbohydrate sources. Within the liver, insulin suppresses the activity of G6Pase, preventing the export of glucose. Thus the net effect of insulin is to dramatically decrease plasma glucose by an increased uptake of the circulating sugar, conversion to glycogen and preventing the formation of more endogenous glucose. It is worth noting that the major role of glycogen is different depending on the organ. In the liver glycogen is primarily a source for the homeostasis of plasma glucose levels and is largely hormonally controlled notably insulin and glucagon. Skeletal glycogen stores are sources for energy production *within* the cell where the glycogen is stored; the balance between synthesis and degradation affected by the cell's energy state (high ATP = synthesis, high AMP = degradation); therefore skeletal glycogen has a role in the decrease of serum glucose (as a store) but not as a source for replenishing low plasma levels.

Hormonal prevention of hypoglycaemia

The pathological consequences of low plasma glucose have been discussed above. Hypoglycaemia can also occur as a consequence of an individual with diabetes injecting too much insulin, but fortunately there are mechanisms to minimize this problem. The most basic response is to increase plasma glucose by either ingesting carbohydrates or by increasing *de novo* synthesis of glucose from non-carbohydrate sources such as glycerol (obtained from the breakdown of triglycerides) or glutamine in the kidney. Such a response is also coupled to a decreased uptake of glucose from the blood into skeletal tissue. In a patient without diabetes falls in plasma glucose are usually due to fasting or prolonged exercise that requires high levels of energy to be supplied to the muscles, and hence a greater requirement for the delivery of glucose as the stocks of glycogen held within the cell are depleted. The liver now becomes the focus of much activity, as it is the primary contributor of non-dietary glucose to the blood because of the presence of G6Pase. However, during glycolysis, the end product (pyruvate) may be converted to lactate because of anaerobic respiration instead of entering the oxidative pathway for energy metabolism. The lactate produced will be transported to the liver where it can be converted back to pyruvate (the Cori cycle) and ultimately used to

regenerate glucose by the gluconeogenic pathway. Gluconeogenesis becomes more important during times of fasting and starvation when glycogen is depleted. The kidney, as the other major gluconeogenic organ, producing glucose mainly from the conversion of glutamine, plays a significant role in the maintenance of adequate blood glucose.[5] Indeed, as much as 20% of blood glucose may be renal in origin and after significant fasting (> 4 weeks) the kidney may contribute as much as 50%. Where glucagon output is lost in patients with diabetes the recovery (without assistance from exogenously supplied glucagon) from hypoglycaemia is heavily dependent on the kidney. In healthy individuals glucose production by the kidney is enhanced by epinephrine and inhibited by insulin.

A number of hormones are released in response to decreasing glucose concentrations (Table 1). Catecholamine hormones increase the rate at which glycogen is converted to glucose (by affecting the activity of G6Pase) and the rate glucose is delivered into the blood stream at times of stress, such as during exercise. Other stress-related hormones (e.g. somatostatin and cortisol) also react to a fall in blood glucose. Somatostatin has a multitude of effects that may contribute to normal plasma glucose concentrations: inhibiting release of thyroid stimulating hormone, thus reducing metabolism and the demand for glucose; inhibiting the release of insulin; and possibly lowering the rate of gastric emptying.

The effects of glucagon in the fasting state and the catecholamines during the fight or flight response elevate blood glucose by promoting hepatic gluconeogenesis. Glucagon secretion during declining plasma glucose and stimulation of the pancreatic α-cells by epinephrine and norepinephrine effectively reverse the effects of insulin: promoting the breakdown of glycogen, enhancing the activity of G6Pase, as well as other enzymes in the gluconeogenic pathway, whilst inhibiting the glycolytic pathways. In patients with type 1 diabetes, a reduced ability to respond to hypoglycaemia is often observed. Frequently these patients have an impaired autonomic response that affects the production of glucagon. Their pancreatic α cells may also become less able to produce glucagon due to continuous low concentrations of insulin.

Comment

There are a significant number of regulatory mechanisms controlling the homeostasis of plasma glucose levels that attempt to keep the level within acceptable physiological norms. Failure to do so, as in diabetes has dire consequences leading to further serious health risks such as cardiovascular disease. An understanding of the basic mechanisms, particularly the role of insulin, will help inform further health related topics. The UK is facing an epidemic of type 2 diabetes due to rising levels of obesity that, while insulin is present, there is a net decrease in the system resulting in the inability to regulate glucose levels ultimately leading to major health risks .

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