# 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 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, a 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.

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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, 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 affects 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 found in many cell types, is a constitutive transporter of glucose and is responsible for the supply of a basal level of glucose. It is found in the brain, blood–brain barrier and has an important function for the transport of glucose across epithelial layers (i.e. from the blood stream across the capillary to the target tissue). sGLT-1, 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, sGLT-1 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 sGLT-1 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. GLUT-2, found in liver and kidney cells (but not exclusively), is important because it not only absorbs glucose but can also transport glucose into the blood when plasma concentrations are low.

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-signalling 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 were to continue unchecked. The molar ratio of insulin:glucagon is usually around 2.0. Increases in this ratio (e.g. after a meal) enhance glucose uptake, utilization and conversion to glycogen, whereas decreases in the ratio (due to either decreased insulin or increased glucagon – seen during fasting and prolonged exercise) lead to increased glycogenolysis, gluconeogenesis, and amino acid mobilization, 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 hyperglycaemia, 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, which has the effect of increasing glycogenolysis and elevating serum glucose levels in response to stress. Likewise, import of glucose into β cells by GLUT-2 triggers the production of insulin to mediate a reduction of the plasma glucose load. Pancreatic 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

As mentioned previously, there are a number of pathways for glucose to enter the blood (see Figure 1 for an overview) but, simply put, the source is either dietary or endogenously produced sugar. 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

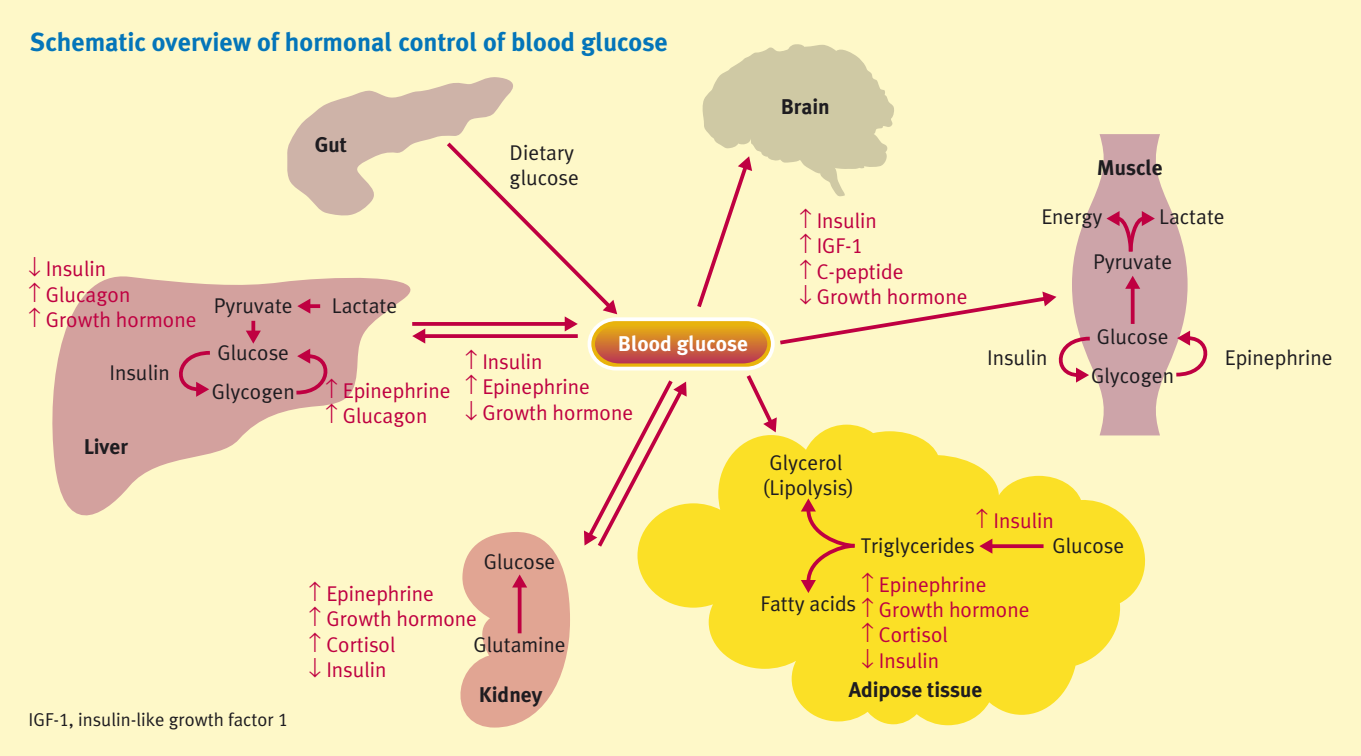


**Figure 1**