Hormonal control of metabolism: regulation of plasma glucose

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Abstract

Blood glucose concentrations are required to be maintained within a narrow therapeutic range in order to ensure the normal functioning of the body. This is accomplished through a complex, interactive, finely coordinated neuro-endocrine regulatory process. Hormonal control through the opposing actions of insulin and glucagon secreted by the islet cells of the pancreas serve as the primary response mechanism to avert post-prandial hyperglycaemia and fasting hypoglycaemia. In addition to this basic response, a range of endocrine mediators concurrently intervene, to enable the fine modulation of the process through a range of insulin-dependent and insulin-independent processes, which ultimately achieve glycaemic control by influencing tissue glucose uptake, glycolysis, glycogenesis, glycogenolysis and gluconeogenesis. More recent evidence supports a central, predominantly hypothalamic role initiated through nutrient (glucose, fatty acid) and hormonal (insulin, leptin, glucagon-like peptide-1) stimuli that influences glucose regulation by direct or indirect effects on skeletal muscle glucose uptake, islet cell insulin/glucagon secretion and hepatic glucose production.

Keywords Brain-islet axis; glucagon; gluconeogenesis; glucose homeostasis; glycogenolysis; insulin; neuro-hormonal regulation

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Learning objectives

After reading this article, you should be able to:

- understand the physiological regulatory processes contributing to the maintenance of steady state glucose homeostasis
- appreciate the role and underlying mechanisms responsible for the pancreatic insulin-glucagon and external modulator response to fluctuations in blood glucose levels
- recognize the complex and dynamic interplay between islet and brain-centred glycoregulatory systems in effecting normal glycaemic control

Introduction

Glucose, an essential nutrient for living organisms, functions not only as rich source of potential energy, but also as a precursor for a wide array of metabolic intermediates in biosynthetic pathways. Plasma glucose levels are required to be maintained within a narrow range to ensure the normal functioning of organs and tissues. The complex regulation of glucose metabolism is effected by a sophisticated network of hormones and neuropeptides released primarily from the pancreas, liver, intestines, brain, muscle and adipose tissue. Glucose enters the blood stream *via* the liver through a range of routes including carbohydrate absorption from the intestines, the breakdown of glycogen (glycogenolysis) or endogenous glucose synthesis (gluconeogenesis). Glucose exits the blood when utilised by many organs and tissue, especially the brain, muscle and adipose tissues. The net effect of the influx and efflux mechanisms result in the maintenance of arterial blood glucose concentrations between 3.5 mmol/litre (after exercise) to 9 mmol/litre (following a meal), while post-prandial levels are confined within a narrow range of 4–5.5 mmol/litre.

Glucose homeostasis is primarily driven by the concurrent, opposing actions of a range of hormone. Insulin promotes the lowering of plasma glucose concentrations and its subsequent conversion to glycogen, while glucagon acts as the main opposing hormone to increase plasma glucose levels by promoting glucose release from the liver through glycogen breakdown. The dynamic interplay between the insulin-glucagon interaction, together with the permissive role of several other hormones (e.g. growth hormone, glucagon-like peptide-1 (GLP-1), leptin, c-peptide etc.), non-glucose fuels (e.g. free fatty acids (FFAs)) and catecholamines, provides the complex modulatory framework requisite for maintaining glucose homeostasis. In spite of these complex interactions, the generic framework of 'normality' being a dynamic balance between forces that tend to increase the value of a given variable and opposing forces that tend to decrease the value of that variable concurrently, very much holds true when applied to glucose homeostasis. The versatility of the regulatory mechanisms is reflected in its ability to respond to the widely varying carbohydrate concentrations that occur after a heavy meal or prolonged fasting, in addition to being able to deliver the immediate energy requirements of intense exercise or survival responses (e.g. flight or fight response). Glucose is the primary source of energy for most tissues, particularly the nervous system, red blood cells, renal medulla and skeletal muscles. A failure in the regulation of this nutrient can result in hypoglycaemia and hyperglycaemia, with dire clinical consequences including death. It is in fact established that the brain may suffer irreversible damage even after a very brief period of energy depletion, a concern of great importance in anaesthetized or unconscious subjects.

Absorption and transport of glucose

The entry of glucose into cells is by facilitated diffusion *via* transmembrane glucose transporters (GLUT). GLUT-1, the commonest isoform is ubiquitously present in many cells and is primarily responsible for ensuring the basal glucose needs of the

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cells. This form of transport is dependent on a concentration gradient and the rapid metabolism of glucose ensures that intracellular levels are relatively lower than plasma concentrations. The human genome encodes for 12 passive glucose transporters. GLUT-2 is primarily responsible for the transport of glucose out of hepatocytes when breakdown of glycogen occurs. GLUT-4 is a transporter found in adipose tissues, skeletal and cardiac muscles and its activity is regulated by insulin. The GLUT-4 isoform translocates to the plasma membrane from an intracellular compartment in response to insulin and muscle contractions, resulting in increased glucose uptake in response to high blood glucose concentrations.

Pancreatic regulation of glucose metabolism

The pancreas plays a dominant role in the regulation of glucose metabolism by secreting the two key opposing hormones, insulin and glucagon, which are responsible for lowering and increasing glucose levels respectively. The major portion of the pancreas is formed from acinar or exocrine cells which secrete digestive hormones into the duodenum, *via* the pancreatic and accessory pancreatic ducts. The endocrine function of the pancreas relates to cell clusters called the islets of Langerhans which reside within the exocrine tissue and account for 1–2% of the organ by mass. Five distinct endocrine cell populations reside within the islets of Langerhans and produce varying hormones (Table 1).

Insulin is a polypeptide hormone secreted by the β-cells of the islets in response to high blood glucose levels. Glucose uptake by β-cells is through facilitated diffusion using the transporter GLUT-2 located on the cell surface. Within the cells the glucose undergoes glycolysis with ATP generation, which in turn results in closure of the ATP-sensitive K^+ channels (K_{ATP} channels). The resultant decrease in the outward movement of K^+ elicits depolarization of the cell membrane and the opening of voltage-dependent Ca^{++} channels (VDCCs). Insulin is stored in large core-dense vesicles within the β-cells. Increased intracellular Ca^{++} levels are detected by a family of sensorproteins, synaptotagmins, which in turn form a complex with synaptosomal-associated receptor proteins (SNAREs) to trigger the fusion of the insulin vesicles with the plasma membrane and the release of the hormone into the extracellular environment through exocytosis. Following glucose stimulation, the insulin precursor proinsulin is cleaved to form equal amounts of insulin and connecting peptide (C-peptide). Although the role of C-peptide is as yet unclear, there is evidence to suggest that it might influence glucose uptake in skeletal muscles in a dose dependent manner. Furthermore, plasma C-peptide levels are often monitored as a surrogate marker of glucose stimulated insulin secretion. Insulin release from β-cells is biphasic, with a major peak within the first 5 minutes of a glucose stimulus follow by a slower smaller peak.

Insulin promotes glucose uptake in tissues, particularly the skeletal muscles, liver and adipose tissues. The transport of glucose molecules across the sarcolemma of skeletal muscles which account for approximately 40% of the body mass, therefore, play a crucial role in regulating blood glucose levels. While both GLUT-1 and GLUT-4 mediate the facilitated diffusion of glucose molecules in an insulin sensitive manner, the latter has emerged the dominant isoform in the process, particularly during periods of increased insulin sensitivity, as is the case after following active muscular exercise. However, not all tissues are insulin sensitive. In the liver and pancreas for example, glucose transport is also mediated through GLUT-2 receptors which do not respond to changes in insulin levels. Similarly, glucose uptake in the brain is mediated through GLUT-2 which does not translocate to the plasma membrane in an insulin sensitive manner. Indeed, such an insulin-independent mechanism is key to for glucose homeostatic control outside the function of fuel utilisation, including glucose sensing and maintenance of basal glucose levels.

The plasma membrane of hepatocytes is freely permeable to glucose transport permitting a rapid response to any perturbations of blood glucose levels. Increases in insulin levels trigger a signalling pathway which entails the binding of insulin to the insulin receptor and the activation of the canonical insulin receptor substrate (IRS)-phosphatidylinositol 3-OH (PI3K)-Akt pathway. This results in the suppression of hepatic glucose production (HGP) by the inhibition glycogenolysis (the breakdown of glycogen to glucose) and the stimulation of hepatic gluconeogenesis (the synthesis of new glucose from non-carbohydrate carbon substrates). In addition, glycolysis and glycogenesis are triggered within hepatocytes, further aiding the shifting of the glucose load from the plasma into the hepatocytes either for oxidation or for storage as glycogen. A second pancreatic hormone, somatostatin, released by the δ cells of the pancreatic islets in response to high plasma glucose, amino acids and fatty acids, contributes to glucose homeostasis by acting as an inhibitor of insulin secretion.

Accurate glycaemic control by the islets is very much dependent on the opposing arm of the regulation involving a second hormone glucagon. In contrast to insulin, glucagon release by α cells of the pancreatic islets is triggered by a reduction in blood glucose levels. Glucagon opposes hypoglycaemia by mobilizing glucose into the plasma through increased glycogenolysis and gluconeogenesis. In addition, the simultaneous inhibition of the intra-hepatic glycolysis and glycogenesis impedes further glucose uptake by hepatocytes (Figure 1). The islet centred model for glycaemic control proposes that the regulatory process is initiated primarily by the effect of high levels of blood glucose.

Cell populations in the islets of Langerhans, hormones and functions

	% islet cells	Endocrine hormone	Function
α-cells	15–35	Glucagon	Increases blood glucose levels
β-cells	55–80	Insulin	Decreases blood glucose levels
γ-cells	3–5	Pancreatic polypeptide	Regulates exocrine and endocrine function of the pancreas
δ-cells	3–10	Somatostatin	Inhibits insulin and glucagon release
ε-cells	<1	Ghrelin	Regulates apetite

Table 1